Xolair® (omalizumab) for Subcutaneous Use

Pediatric (6 to < 12 years) Efficacy Supplement

United States Food and Drug Administration
Pulmonary-Allergy Drugs Advisory Committee

November 18, 2009 (draft)

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Introduction/Background

Peter Fernandes, MPharm

Vice President
Drug Regulatory Affairs, Respiratory
Novartis Pharmaceuticals Corporation

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Overview

- Xolair® Introduction
  - Current indication
  - Proposed indication
- Regulatory history
- Key considerations for Xolair pediatric indication

Xolair®

- Humanized monoclonal antibody
- Designed to inhibit binding of IgE and block the allergic cascade
- Subcutaneous injection of 150 - 375 mg
- Administered every 2 to 4 weeks in a healthcare setting

Xolair® Approved Indication (2003)

Xolair (omalizumab) is indicated for adults and adolescents (12 years of age and above)

- Moderate to severe persistent asthma
- Positive skin test or in vitro reactivity to a perennial aeroallergen
- Symptoms inadequately controlled with inhaled corticosteroids
- Xolair has been shown to decrease incidence of asthma exacerbations
- Safety and efficacy are not established in other allergic conditions

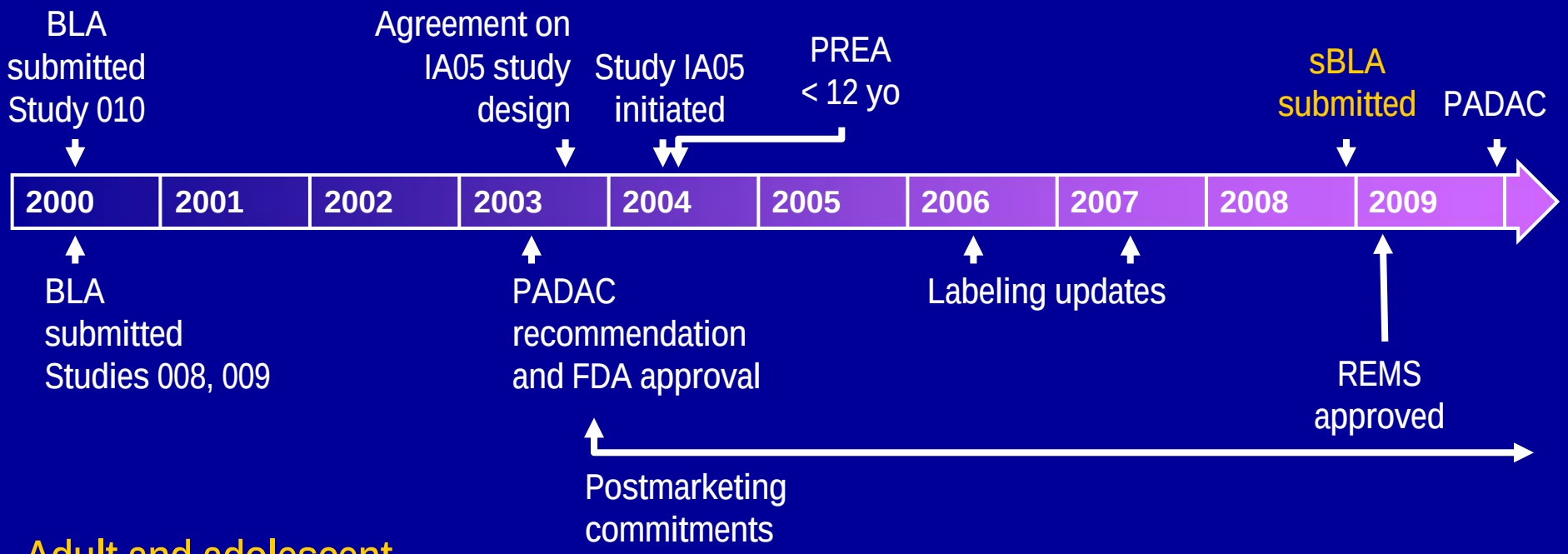
Xolair® Proposed Indication (2009)

Xolair (omalizumab) is indicated for adults and children (6 years of age and above)

- **Moderate to severe persistent asthma**
- **Positive skin test or in vitro reactivity to a perennial aeroallergen**
- **Symptoms inadequately controlled with inhaled corticosteroids**
- **Xolair has been shown to decrease incidence of asthma exacerbations**
- **Safety and efficacy are not established in other allergic conditions**

Xolair® Regulatory History

Pediatric development program



Adult and adolescent development program

Allergy and Moderate-to-Severe Asthma

- Allergy is the most common cause of asthma
- A subset of patients remain uncontrolled despite treatment with multiple therapies
  - Xolair® offers an important treatment option
  - Proposed labeling extension would make this option available to children aged 6 to 11 years

Overview of Sponsor Presentations

- Xolair® is intended for the subset of patients with uncontrolled asthma despite currently available therapy
- Significant reduction in exacerbation rate maintained over time
- Benefits seen in children are consistent with those in adults and adolescents
- No new safety concerns observed in children
- Positive benefit/risk in favor of Xolair

Agenda

Pediatric Allergic Asthma	**George O'Connor, MD** Boston University School of Medicine
Pediatric Development Program	**Robert K. Zeldin, MD** Novartis Pharmaceuticals
Biologic Plausibility of Potential Risk of Malignancy	**Eva C. Guinan, MD** Dana-Farber Cancer Institute Harvard Medical School
Safety Events of Special Interest and Risk Management	**Linda Armstrong, MD** Novartis Pharmaceuticals
Xolair® Clinical Use	**Wayne J. Morgan, MD** University of Arizona

Clinical Experts and Consultants

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- **Donald MacGlashan, Jr., MD, PhD**
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  The Johns Hopkins University

Asthma in Children: Where We Are Today

George O'Connor, MD, MS

Professor of Medicine
Division of Pulmonary, Critical Care, and Allergy
Boston University School of Medicine
Director, Adult Asthma Program, Boston Medical Center

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Overview

- Review current guidelines and medications for the management of childhood asthma
- Describe children whose asthma is inadequately controlled despite guidelines-based management with current therapies

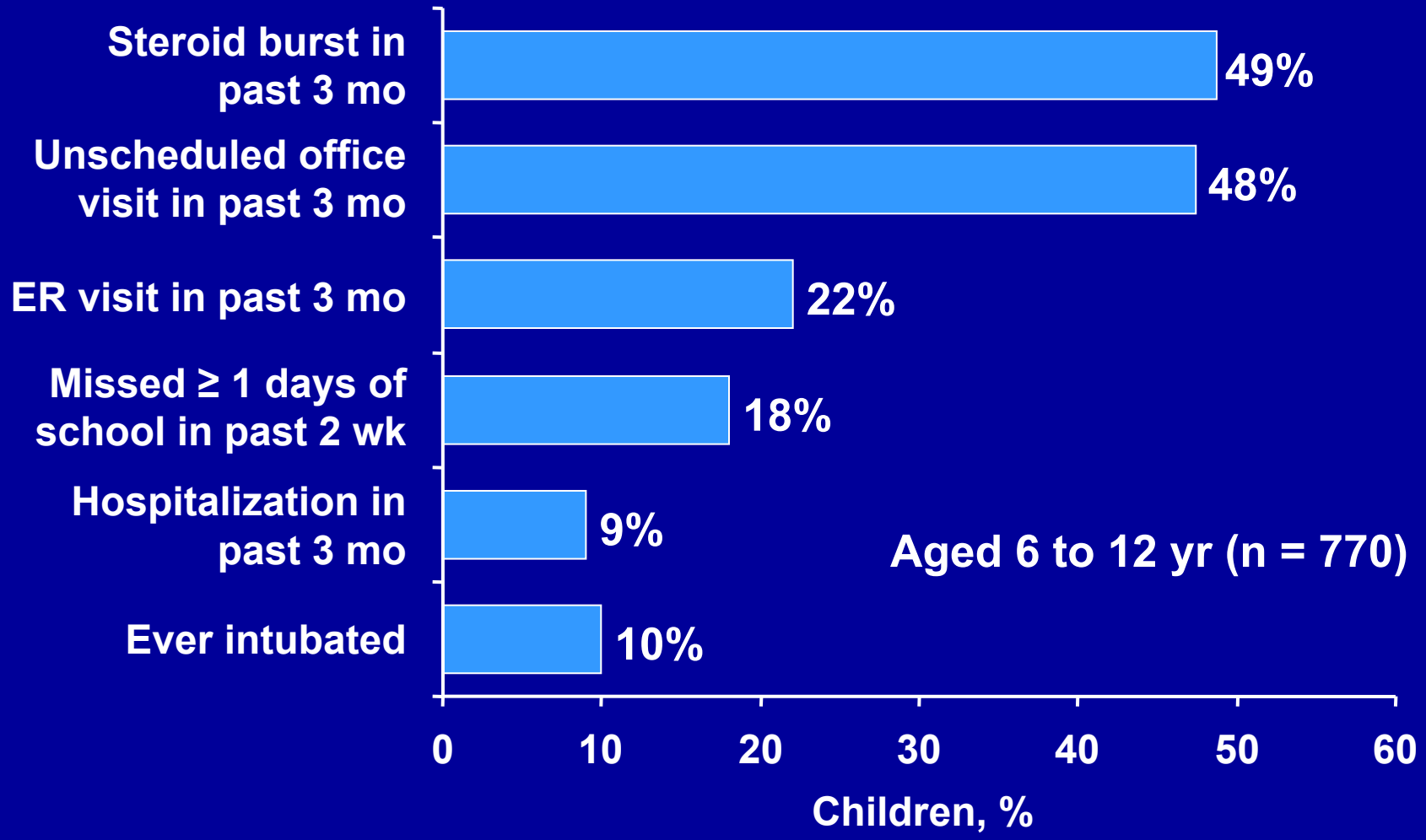
Case Presentation—
10 yo Boy With Severe Persistent Asthma

- Accompanied by allergic rhinitis, eczema, obesity; episodes of otitis and sinusitis
- Followed by pediatric asthma and allergy specialist since age 2
- Hospitalized 7 times through age 3;
  6 times age 3 to 10; many prednisone bursts
- Total IgE = 351; serum eosinophils = 11%
  + specific IgE to mouse, cat, tree pollen
  + mouse infestation of apartment

Case Presentation—
10 yo Boy With Severe Persistent Asthma

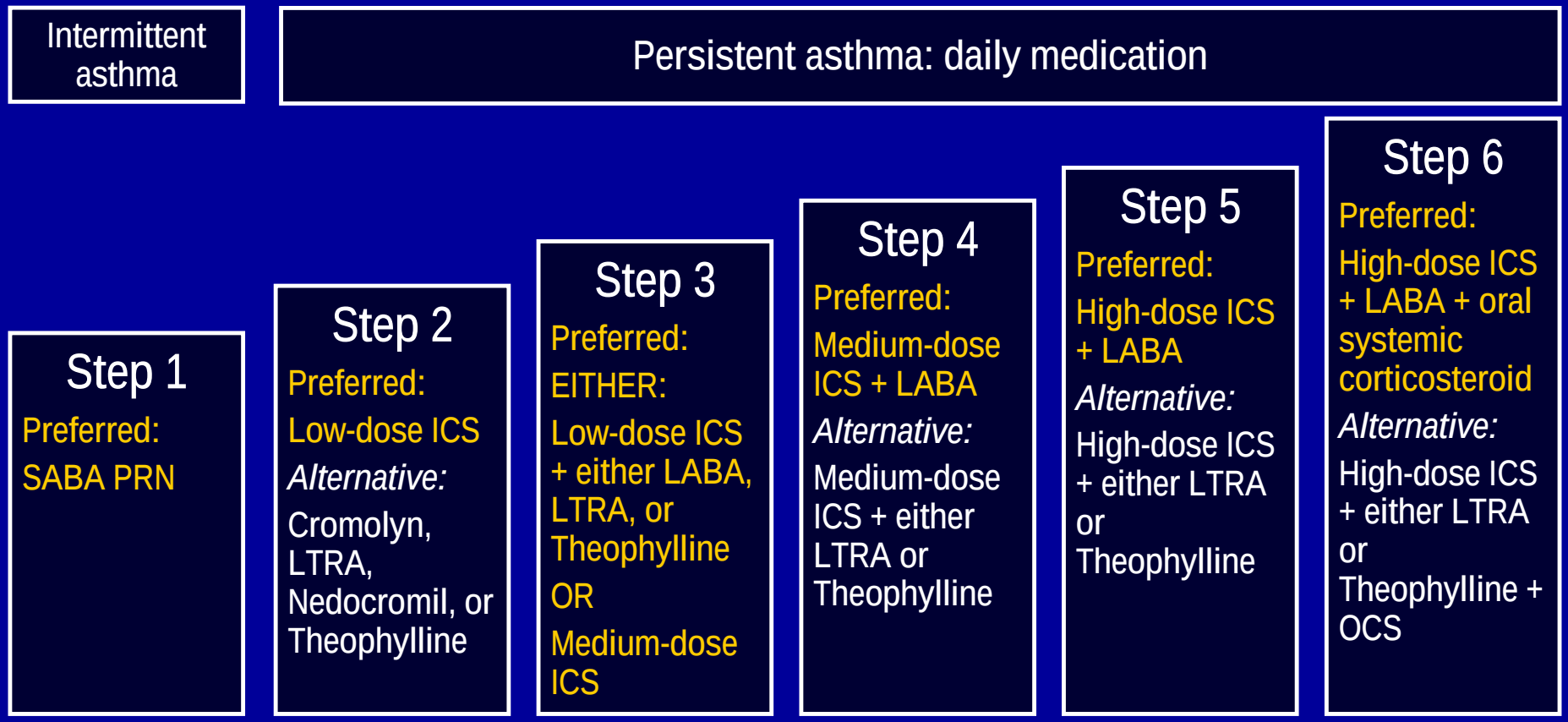
- Current regimen: fluticasone/salmeterol HFA 230/21 2 puffs b.i.d.; montelukast; loratadine; fluticasone nasal spray; PRN albuterol
- Past 12 months: 3 exacerbations, resulting in 1 hospitalization; 2 sick visits; 3 prednisone bursts
- Current status: cough and mild wheeze most days; nocturnal awakenings most nights; FEV_1 = 79% predicted; weight = 84 kg

Children With Difficult-to-Treat Asthma Experience Significant Morbidity



Dolan CM, et al. *Ann Allergy Asthma Immunol*. 2004;92:32-39.

NHLBI 2007 Treatment Guidelines
Stepwise Approach for Managing Asthma in Children 5 - 11 Years of Age



Adapted from NHLBI NAEPP EPR-3: Guidelines for the Diagnosis and Management of Asthma, 2007.

Asthma Control Is Not Achieved in a Small Subset of Children

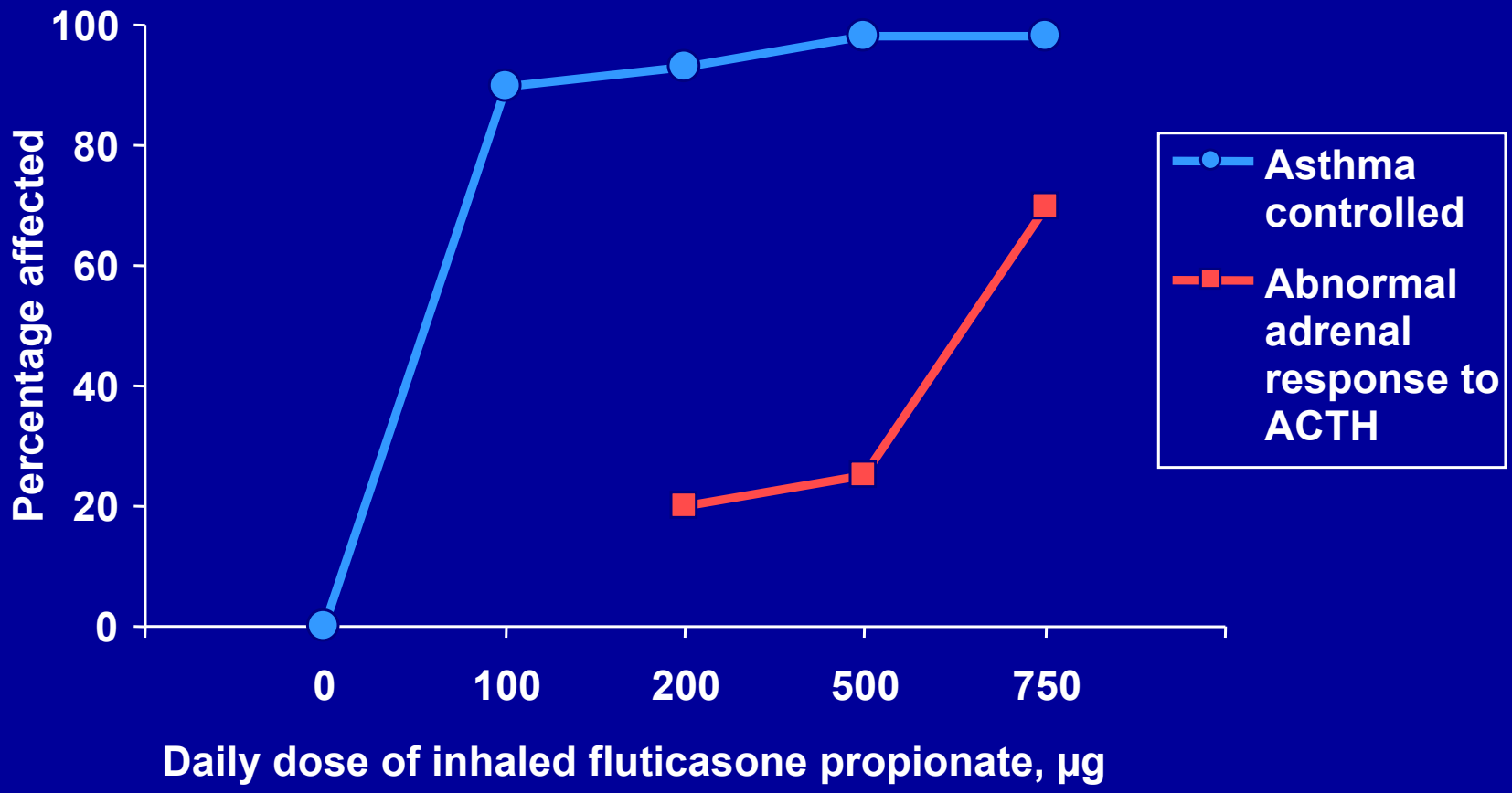
- In a small subset of children, asthma control is not achieved despite pharmacologic treatment recommended in the NAEPP treatment guidelines
- < 6% of asthmatic children are treated with high-dose ICS + LABA combination therapy[a]
- From a general survey of patients, 2% of children with asthma are poorly controlled[b]

[a] IMS prescription data, 2008.
[b] Asthma in America (n = 721, 4 - 18 yr).

Risk/Benefit Issues of Corticosteroid Therapy in Poorly Controlled Asthma

- Frequent or chronic oral corticosteroid therapy
  - Potential side effects include weight gain, impaired bone growth, infection, adrenal insufficiency
- Long-term, high-dose inhaled corticosteroid
  - Safer than systemic corticosteroid, but there is systemic absorption and potential for side effects noted above
  - With increasing dose, efficacy reaches plateau but side-effect potential may not

Increasing Doses of Inhaled Corticosteroid: Limited Additional Efficacy; Potential for Side Effects



Randell T, et al. *Pediatric Drugs*. 2003;5:481-504.

Other Treatment Options

- Long-acting beta agonists (LABAs)[a]
  - Possible increased risk of severe exacerbations
  - ICS-LABA combination fails to control asthma in some children
- Leukotriene receptor antagonists[a]
  - Not adequately studied as adjunctive therapy in children < 12 years old with moderate-severe asthma
  - Modest efficacy in difficult-to-control asthmatic children
- Theophylline[b]
  - Narrow therapeutic window
  - Requires dose titration and monitoring of serum levels
  - Modest efficacy in difficult-to-control asthmatic children

[a] NHLBI 2007.
[b] Tee AK. *Cochrane Database Syst Rev*. 2007;(3):CD001281.

Summary

- Asthma control is achievable in most children
- A small proportion of asthmatic children are poorly controlled despite currently available treatments
- These children experience high morbidity, including frequent exacerbation
- Alternative treatments are needed for patients not well controlled by current asthma therapies, including inhaled corticosteroids

Efficacy and Safety of Omalizumab in the Treatment of Children With Moderate-Severe Persistent Allergic Asthma Inadequately Controlled With Inhaled Corticosteroids

Robert K. Zeldin, MD

Vice President & US Medical Franchise Head
Respiratory and Dermatology
Novartis Pharmaceuticals Corporation

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Presentation Outline

- Pediatric clinical development program
- Efficacy
  - Pivotal Study IA05
  - Supportive Study 010
- Safety
  - Pooled data
  - Adverse events of special interest
- Conclusions

Clinical Development Program in Children 6 to < 12 Years of Age

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Pediatric Clinical Development Program

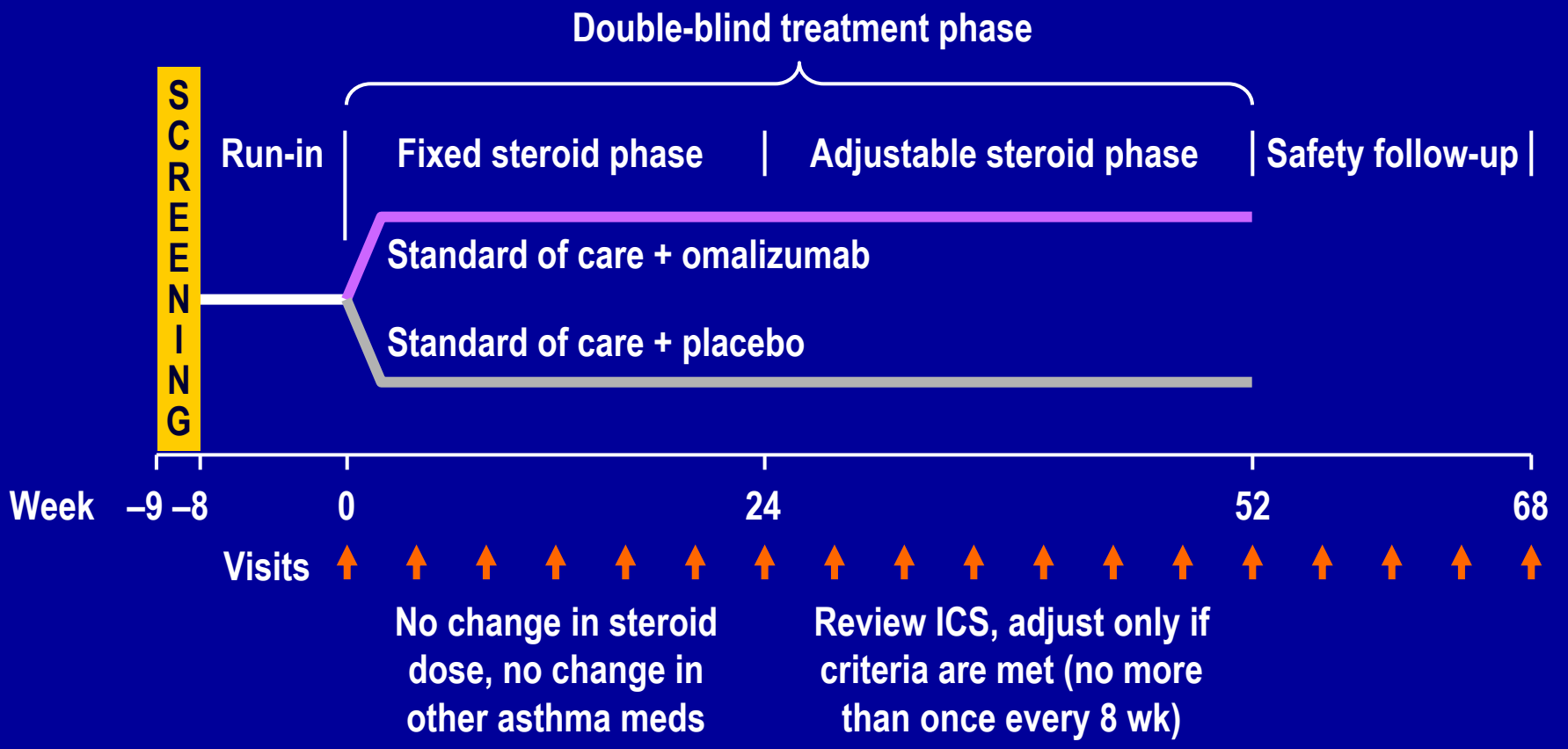
	Patients, n
Study IA05	628
Study 010	298
10 other studies	291
Total number of children 6 - < 12 years old in clinical trials	1217
Total number of children receiving omalizumab	914

FDA SCS Tables 1-1, 1-2, 1-3; Table 1.2-1d

Pivotal Phase III Study IA05

- 1-year, randomized, double-blind, parallel-group, placebo-controlled, multicenter study
- Evaluated efficacy, safety, PK, and PD of omalizumab
- Children 6 to < 12 years
- Moderate-severe, persistent, inadequately controlled allergic asthma

Study Design
Study IA05



Primary Objectives
Study IA05

- Effect of omalizumab on the clinically significant asthma exacerbation rate (24-wk, double-blind, fixed steroid treatment)
- Safety of omalizumab (52-wk, double-blind treatment period and 16-wk follow-up period)

Secondary Objectives
Study IA05

- 52-wk treatment period
  - Clinically significant asthma exacerbation rate
- 24-wk fixed steroid treatment period
  - Change in nocturnal clinical symptom score
  - Change in β-agonist rescue medication use
  - Change in quality of life

Dosing
Study IA05

- Individualized dosing based on
  - Body weight 20 - 150 kg
  - Total serum IgE 30 - 1300 IU/mL
- Dosing designed to deliver a dose of 0.016 mg/kg per IU of IgE per mL
- Doses of 75 - 375 mg administered every 2 or 4 weeks in a healthcare setting

Key Inclusion Criteria
Study IA05

- Patients with allergic asthma
  - ≥ 1 year
  - Total serum IgE ≥ 30 to ≤ 1300 IU/mL
  - Body weight 20 - 150 kg
  - Positive skin-prick test to ≥ 1 perennial aeroallergen
  - ≥ 12% increase in FEV_1 after short-acting beta agonist
- History of exacerbations while receiving fluticasone DPI ≥ 200 mcg/day or equivalent, with or without other controller asthma medications
- Inadequate asthma symptom control during the run-in period despite use of fluticasone DPI ≥ 200 mcg/day or equivalent

Key Exclusion Criteria
Study IA05

- Unable to perform spirometry, peak flow measurements, or complete diary cards
- Unacceptable concomitant medications or non-adherence to medication washouts
- Clinically significant uncontrolled systemic disease or a history of such disease
- Previous use of omalizumab
- History of food- or drug-related anaphylaxis or anaphylactoid reactions
- Platelet levels ≤ 100,000/mL at visit 1
- Diagnosis or history of cancer, investigation for possible cancer

Inadequately Controlled Population Despite High Asthma Medication Use

Study IA05

	Safety population n = 628
Mean age (SD), yr	8.6 (1.7)
Mean duration of asthma (SD), yr	5.7 (2.6)
Gender, n (%) female	203 (32.3)
Mean FEV_1, % predicted (SD)	86.4 (18.0)
Mean serum total IgE (SD), IU/mL	469.7 (338.0)
Mean ICS (SD), µg/day (fluticasone equivalent)	515.1 (285.4)
LABA use, %	67.4
Anti-leukotriene, %	36.6
Mean daily puffs of short acting β_2-agonist (SD)	2.8 (2.6)

Study IA05 Identified a Population With High Unmet Medical Need

- On average 2.6 clinically significant asthma exacerbations per patient per year
- 77% of patients had nighttime awakenings requiring rescue medication use more than once per week
- 76% of patients had daytime symptoms causing at least some discomfort and limiting activities in 4 weeks prior to randomization

Exacerbations Were Clinically Meaningful Events

Study IA05—52-Week Period

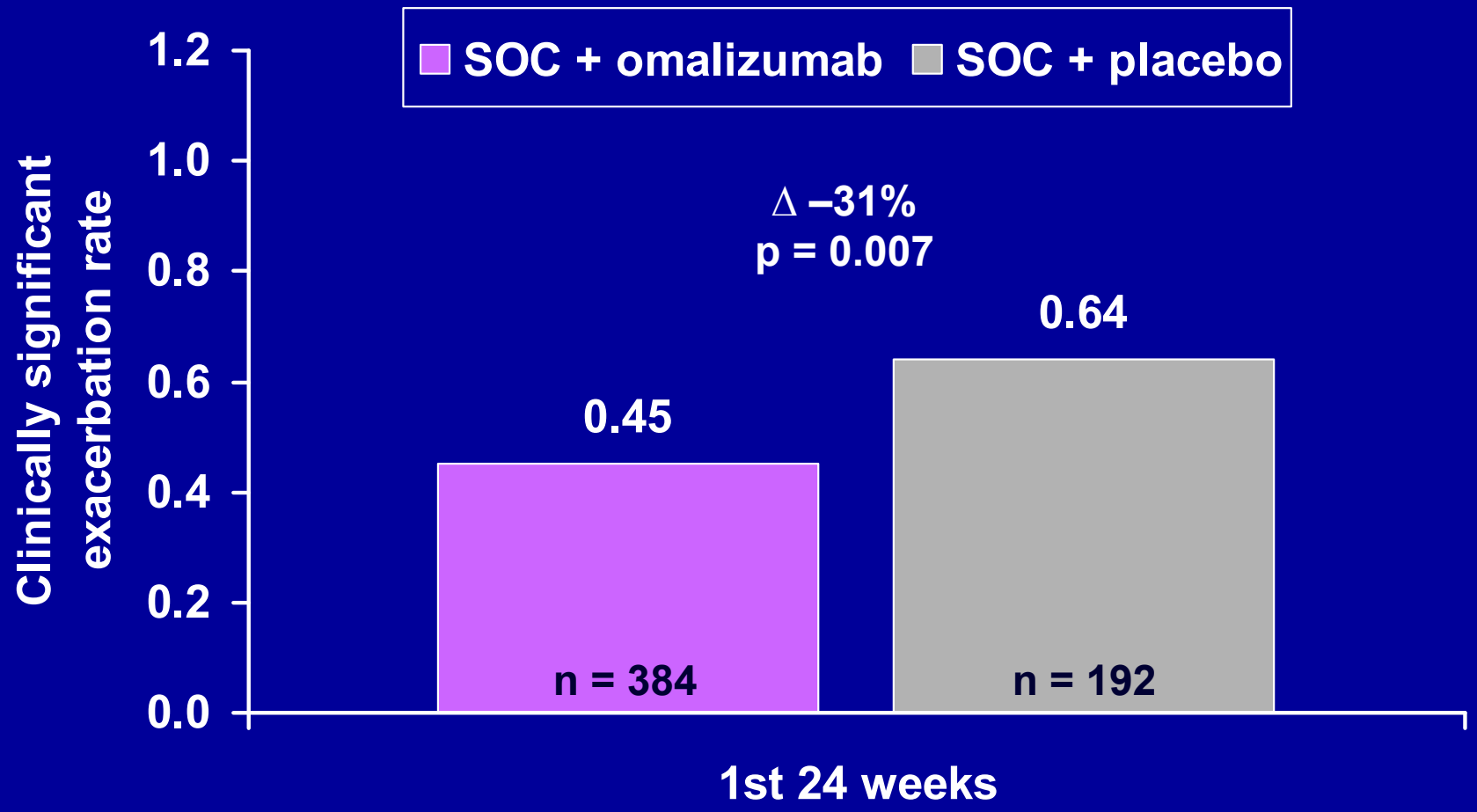
- **Clinically significant** asthma exacerbation defined as a worsening of asthma symptoms as judged clinically by investigator, requiring doubling of baseline inhaled corticosteroid dose for ≥ 3 days and/or treatment with rescue systemic (oral or i.v.) corticosteroids for ≥ 3 days

Exacerbation criteria	%
PEF or FEV_1 < 60% of personal best	25%
PEF or FEV_1 60% - 80% of personal best following β-2 agonist administration	23%
PEF < 80% of personal best on 2 of 3 days	40%
> 50% increase in rescue medication use on 2 of 3 days	59%
2 nighttime awakenings in previous week	62%

Most exacerbations met ≥ 1 criterion.

Primary Endpoint—Exacerbations Are Reduced at 24 Weeks

Study IA05



SOC = Standard of care.

Primary Endpoint—Exacerbations Are Reduced at 24 Weeks

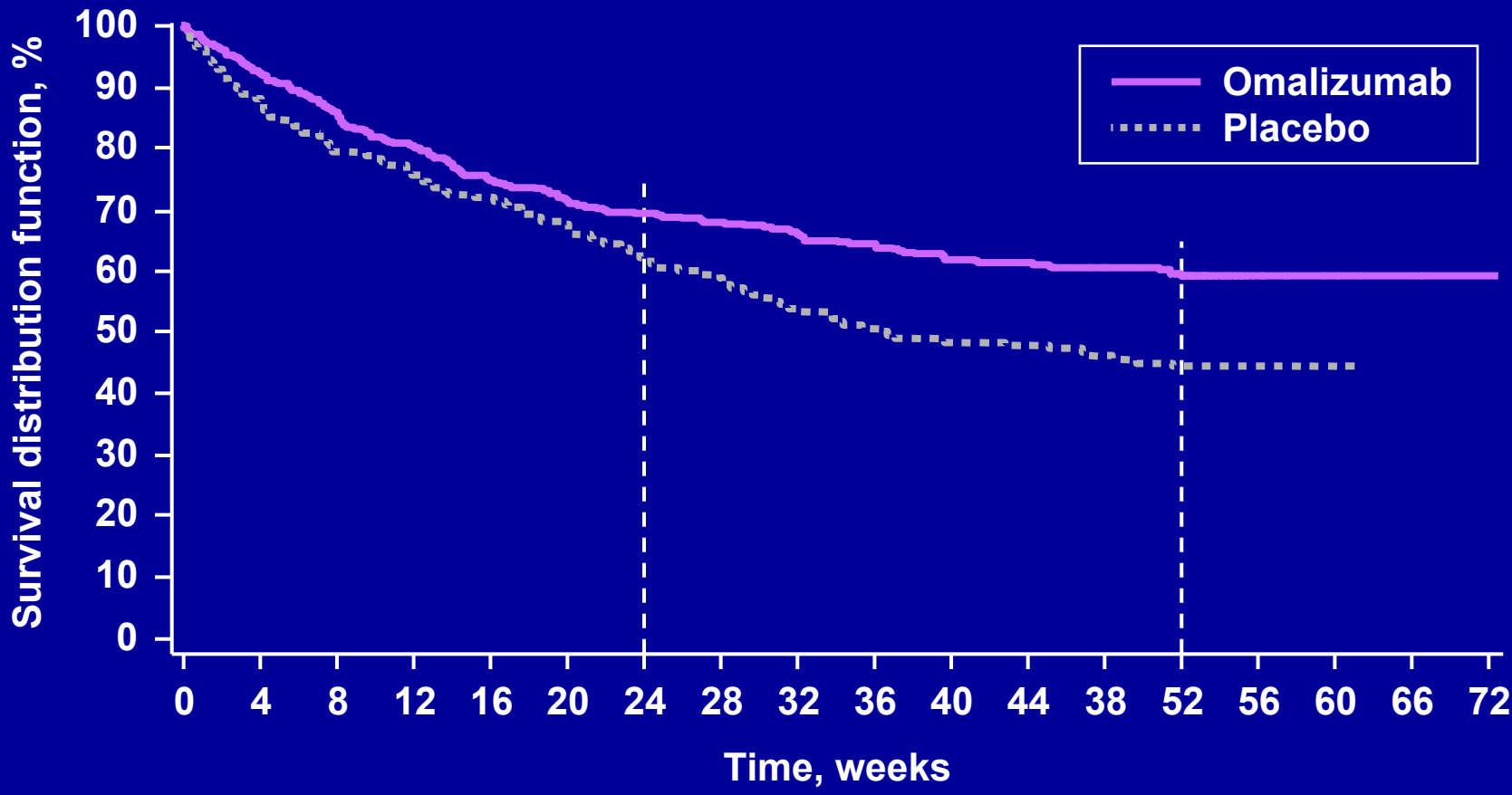
Study IA05

	Omalizumab n = 384	Placebo n = 192
Rate of clinically significant asthma exacerbations per treatment period	0.45	0.64
Omalizumab/placebo	0.693	
95% confidence interval	(0.533, 0.903)	
p value	0.007	
Frequent clinically significant AEEs, n (%)		
0	274 (64.3)	112 (58.3)
1	86 (22.4)	41 (21.4)
2	38 (9.9)	23 (12.0)
3	9 (2.3)	12 (6.3)
≥ 4	4 (1.0)	4 (2.1)

AEE = Asthma exacerbation episode.

Kaplan-Meier Plot of Time to First Clinically Significant Asthma Exacerbation

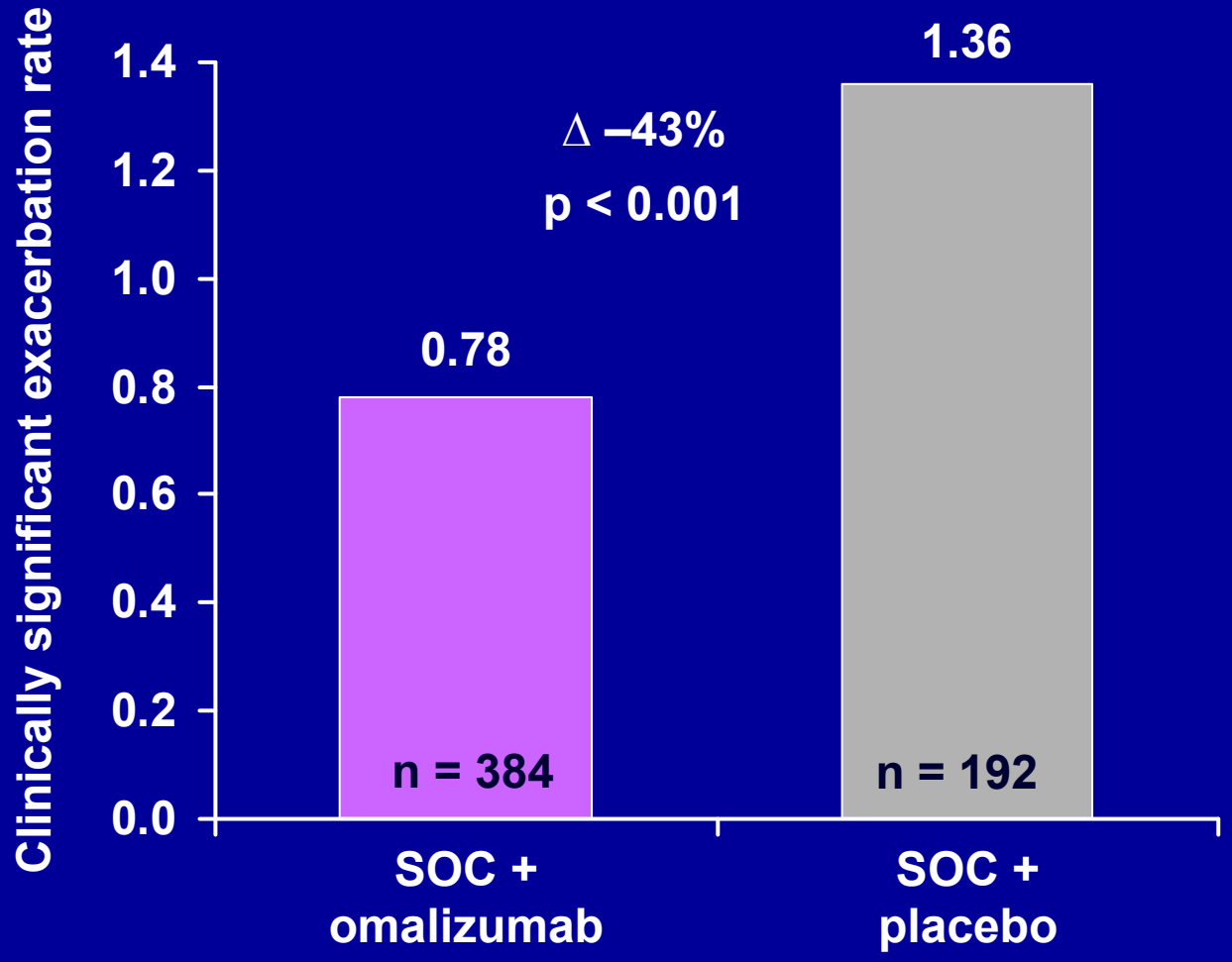
Study IA05



Source: Figure 14.2-1.1

Secondary Endpoint—Reduction in Exacerbation Rate Sustained at 52 Weeks

Study IA05

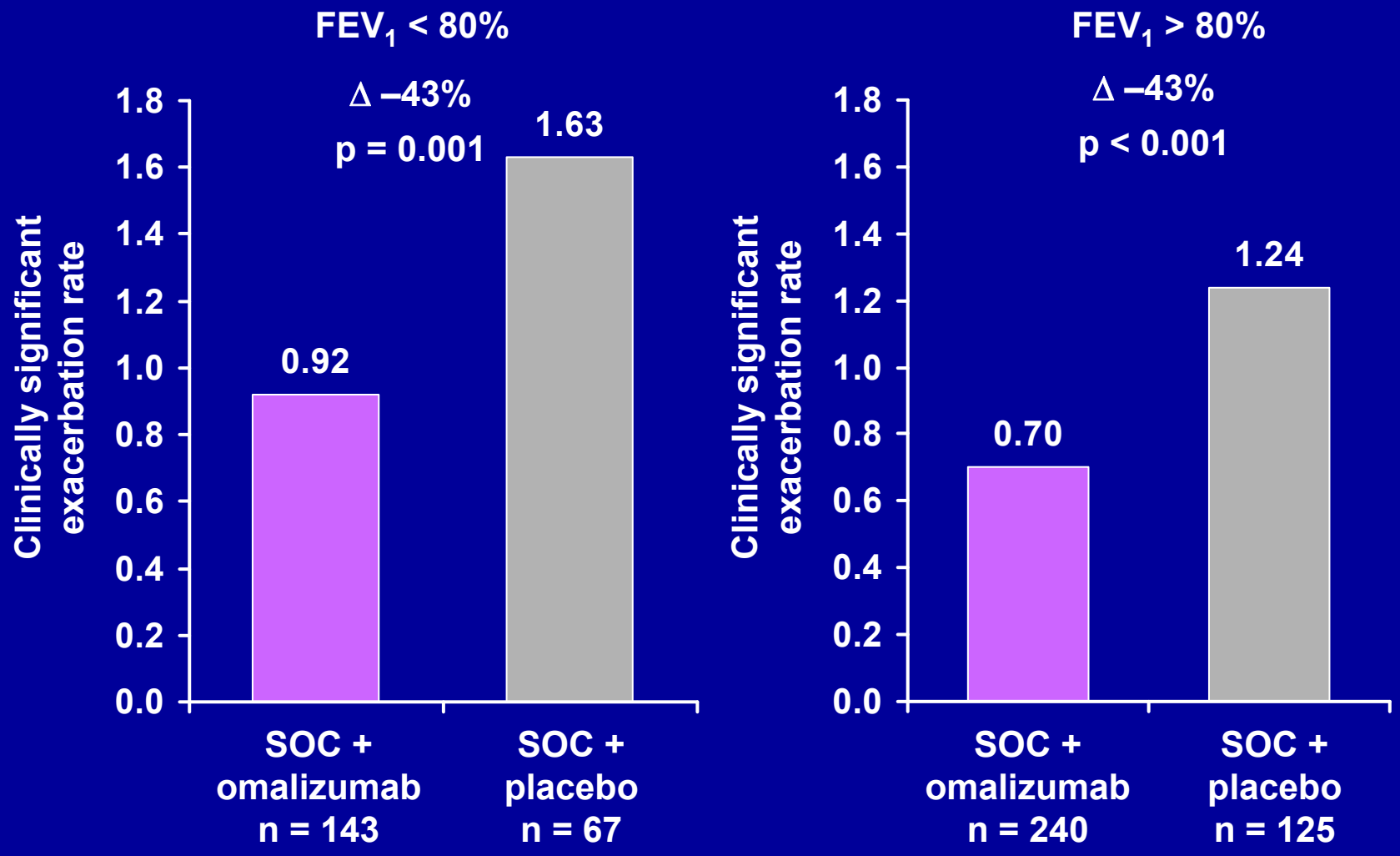


SOC = Standard of care.

IA05 Table 14.2-2.1a

Consistent Reduction In Asthma Exacerbation Rate Irrespective of Baseline Lung Function

Study IA05—52-Week Data



SOC = Standard of care.

Severe Exacerbation and Hospitalization Rate
Study IA05—52-Week Data

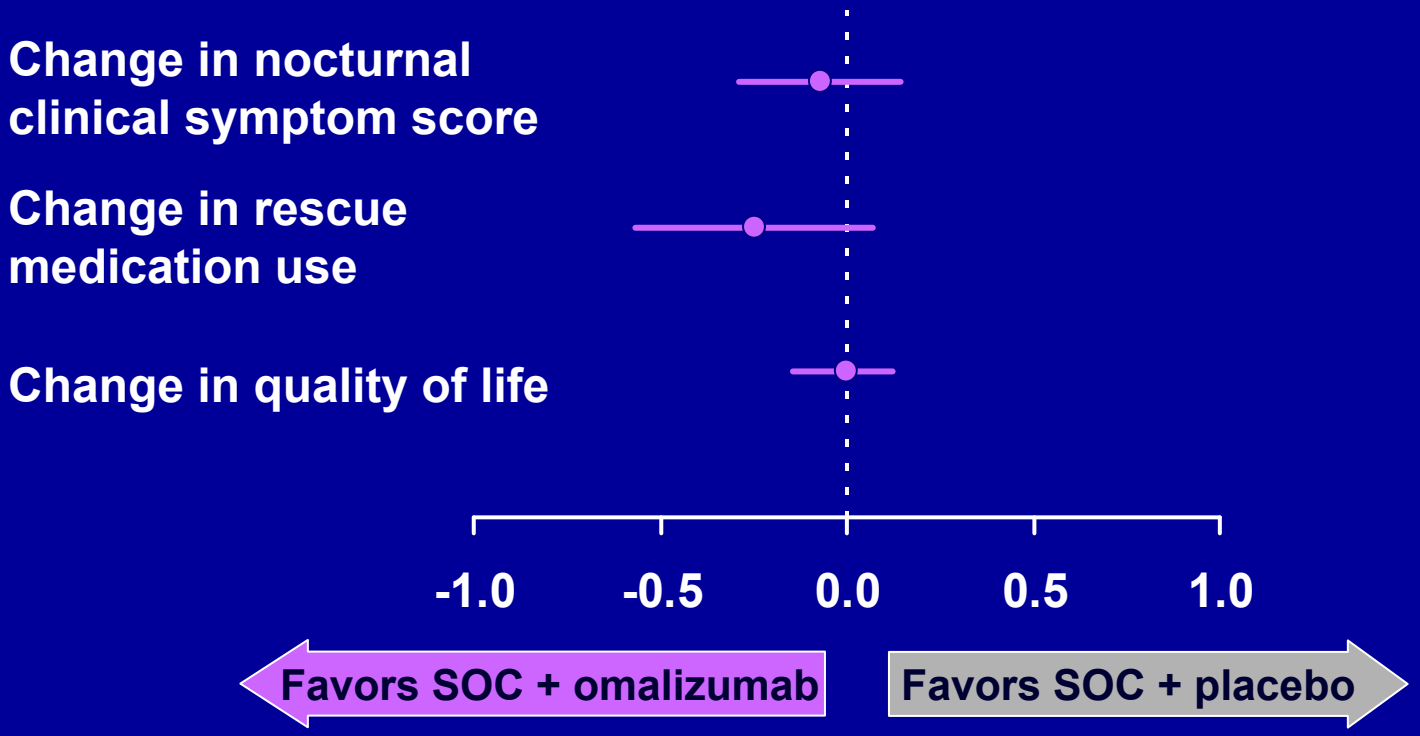
	SOC + omalizumab n = 384	SOC + placebo n = 192	Reduction compared with placebo, %
Severe exacerbation rate	0.12	0.24	50% p = 0.004
Hospitalization rate	0.07	0.13	47% p = 0.085

- Severe exacerbation: Peak Expiratory Flow Rate or FEV_1 < 60% of personal best and required treatment with systemic corticosteroids

SOC = Standard of care.

IA05 Tables 14.2-2.10, 14.2-2.11

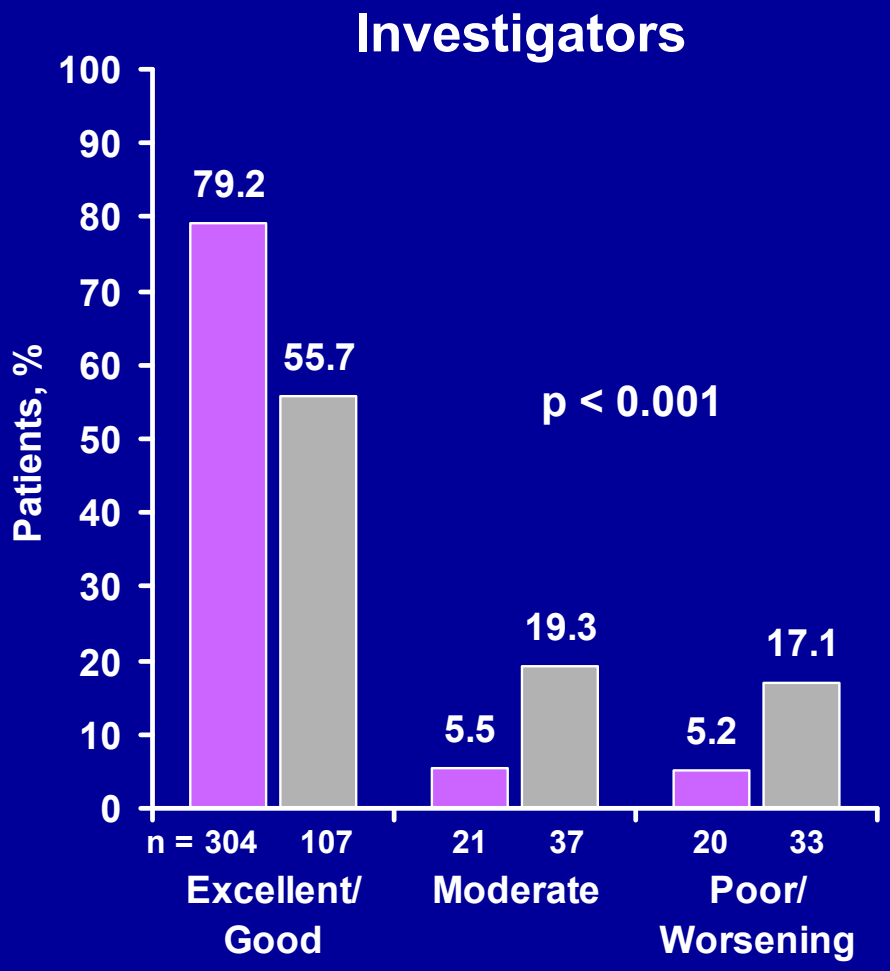
Other Secondary Endpoints
Study IA05—52-Week Data

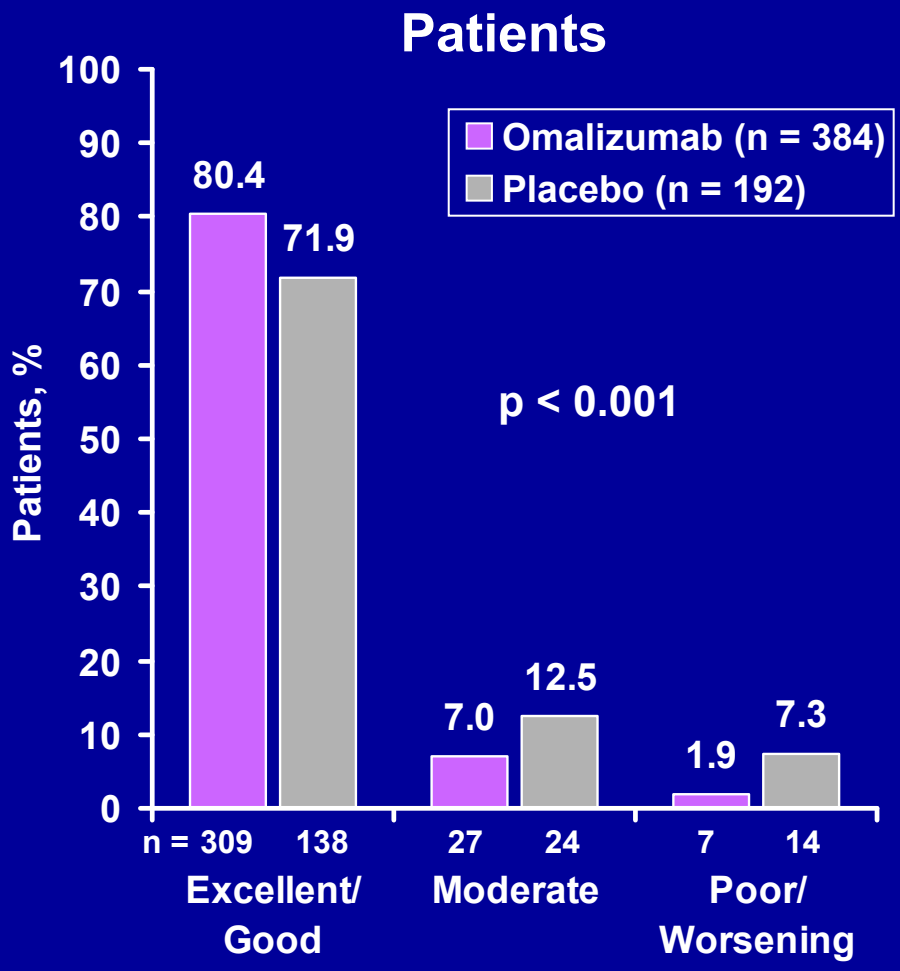


SOC = Standard of care.

Investigator and Patient Global Evaluation of Treatment Effectiveness at 52 Weeks

Study IA05





Briefing doc Table 6-12

Omalizumab-Treated Patients Required Fewer Days of Asthma Rescue Medication

Study IA05—52-Week Data

	SOC + omalizumab n = 384	SOC + placebo n = 192
Mean days, n	115.5	140.3
p value	0.007	

24 fewer days requiring rescue medication

SOC = Standard of care.

Source: Study IA05 CSR Post-Text Table 14.2-4.7

Omalizumab Decreased Systemic Steroid Burden

Study IA05—52-Week Data

	SOC + omalizumab (n = 384)	SOC + placebo (n = 192)
Total systemic steroids (SD) mean mg per patient	233.5 (856.63)	316.7 (661.96)
p value	0.006	

26% less systemic corticosteroid

SOC = Standard of care.

Supportive Phase III Study 010

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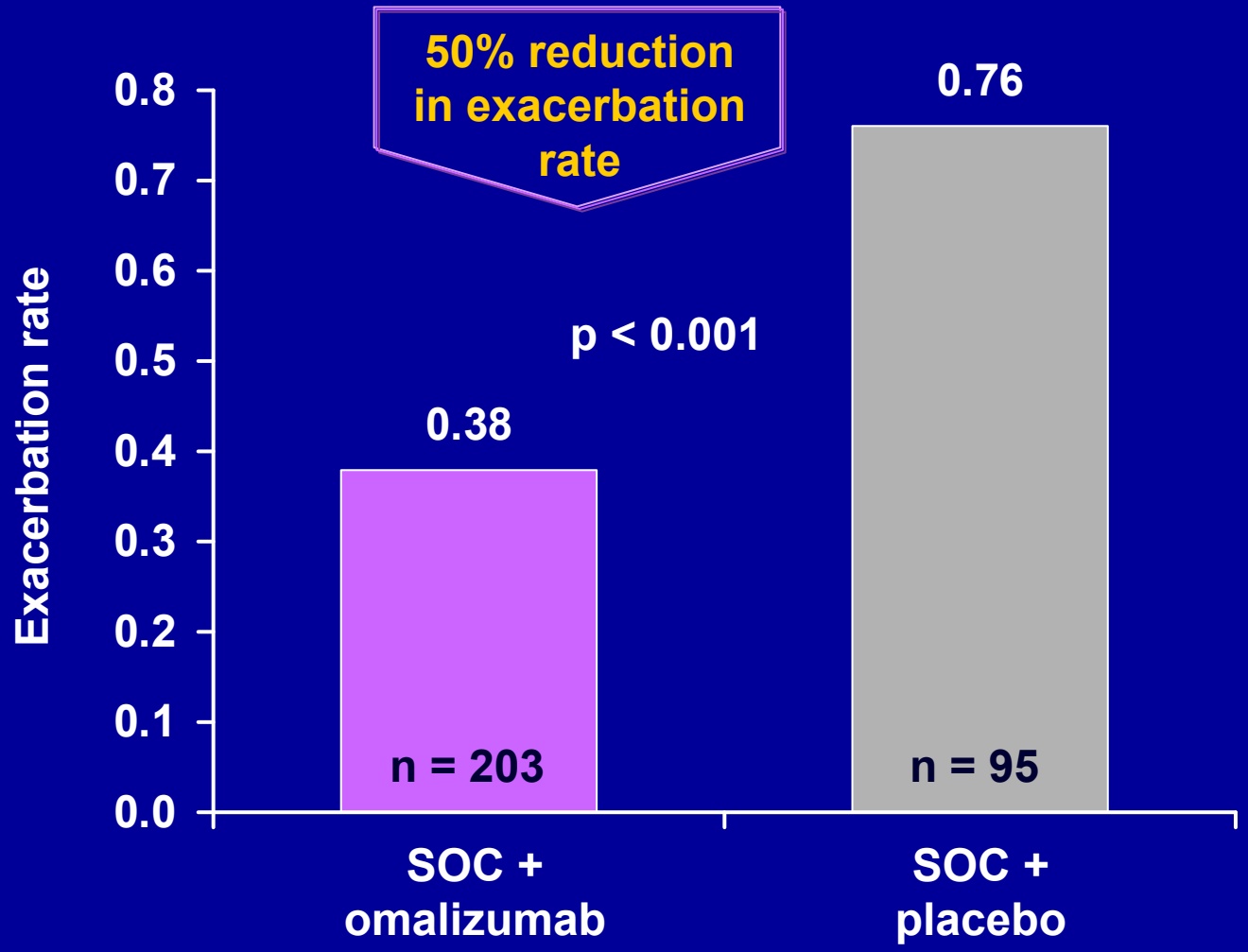
Supportive Phase III Study 010

- 1-year multicenter safety study in children 6 - 12 years with allergic asthma requiring daily treatment with ICS
  - 7-month, double-blind, randomized, parallel-group, placebo-controlled phase
  - 5-month, open-label extension

Patient Demographics
Study 010

Characteristic	All patients N = 298
Mean age, yr (range)	9.1 (5 - 11)
Gender, n (%) female	92 (30.9)
Race, n (%)	
Caucasian	225 (75.5)
Black	48 (16.1)
Oriental	3 (1.0)
Other	22 (7.4)
Mean FEV_1 % predicted (range)	84.2 (43 - 129)
Mean serum total IgE, IU/mL (range)	343.2 (20 - 1269)
Mean ICS, ug/day (fluticasone equivalent) (range)	165.1 (100 - 400)

Exacerbation Rate at 28 Weeks
Study 010



SOC = Standard of care.

Pediatric Safety Profile

Safety Database in Pediatric Clinical Development Program

	Patients (n)
Study IA05	628
Study 010	298
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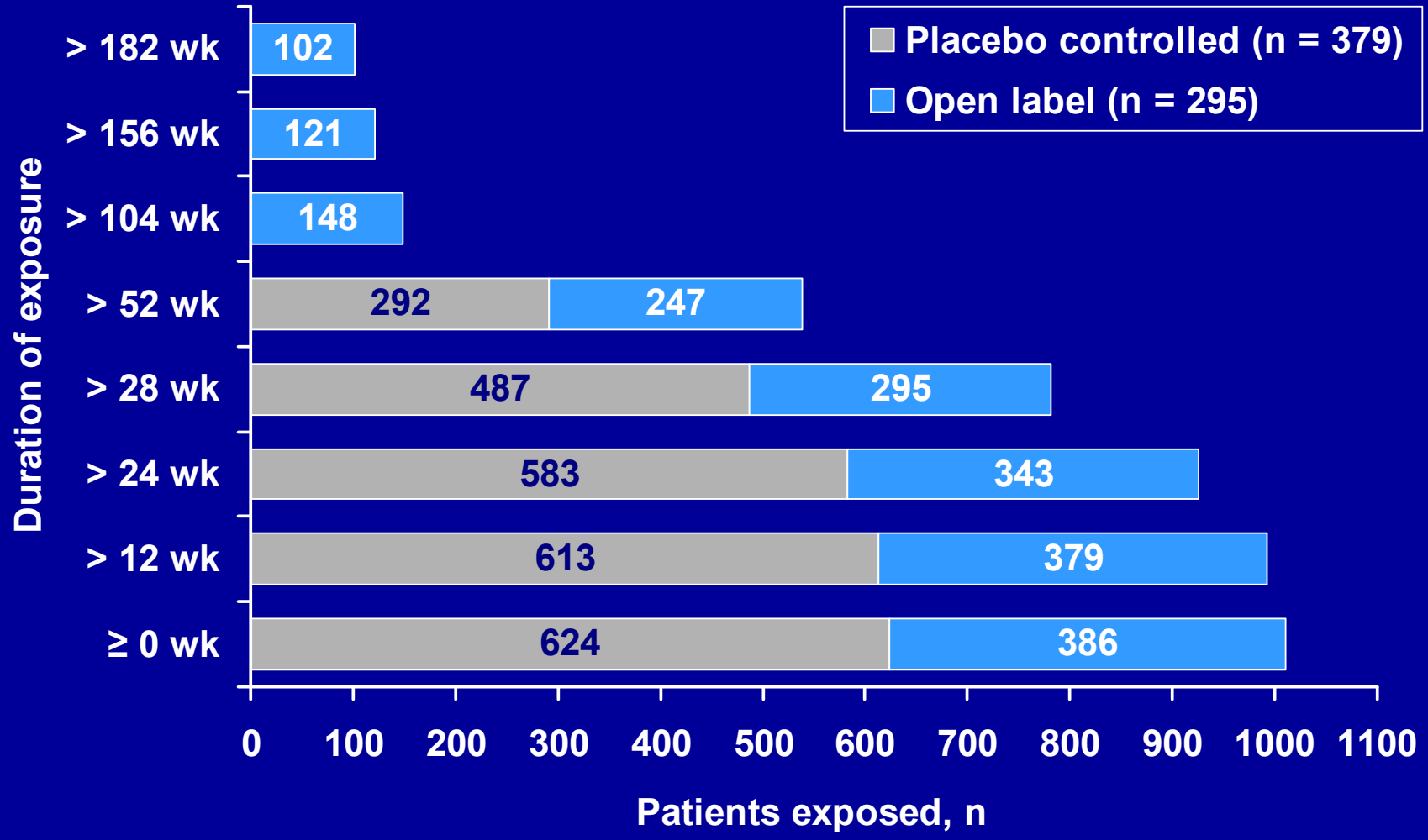
Total number of children 6 - <12 years old in clinical trials	1217
Total number of children receiving omalizumab	914

FDA SCS Tables 1-1, 1-2, 1-3; Table 1.2-1d

Omalizumab Pediatric Clinical Development Program—Duration of Exposure

Allergic Asthma Studies



FDA SCE Table 1-2.1a, 1-2.1c

Most Frequently Affected System Organ Classes in Placebo-Controlled Allergic Asthma Studies[a]

Primary system organ class	Patients, n (%)	
	SOC + omalizumab n = 624	SOC + placebo n = 302
Infections and infestations	480 (76.9)	253 (83.8)
Respiratory, thoracic, and mediastinal disorders	199 (31.9)	104 (34.4)
Gastrointestinal disorders	166 (26.6)	79 (26.2)
Nervous system disorders	148 (23.7)	69 (22.8)
General disorders and administration site conditions	122 (19.6)	59 (19.5)
Skin and subcutaneous tissue disorders	104 (16.7)	46 (15.2)
Injury, poisoning, and procedural complications	92 (14.7)	41 (13.6)
Musculoskeletal and connective tissue disorders	55 (8.8)	29 (9.6)
Eye disorders	33 (5.3)	27 (8.9)
Ear and labyrinth disorders	25 (4.0)	17 (5.6)
Immune system disorders	24 (3.8)	16 (5.3)
Psychiatric disorders	16 (2.6)	12 (4.0)
Blood and lymphatic system disorders	8 (1.3)	9 (3.0)

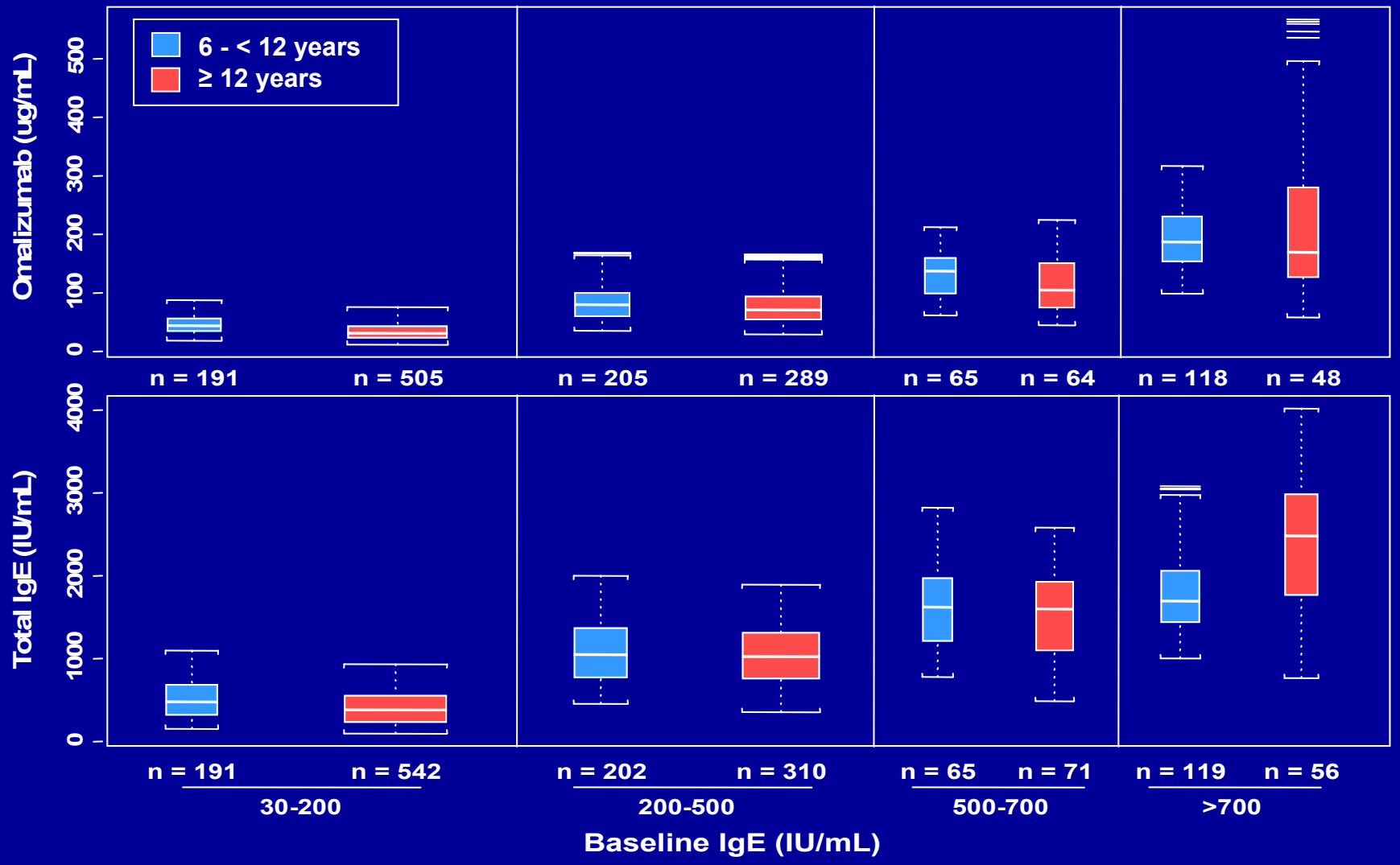
SOC = Standard of care.
[a] ≥ 3% of patients in either group.

Serious Adverse Events in Placebo-Controlled Allergic Asthma Studies[a]

Preferred terms	Patients, n (%)	
	SOC + omalizumab n = 624	SOC + placebo n = 302
Patients with any SAE	21 (3.4)	20 (6.6)
Appendicitis	4 (0.6)	1 (0.3)
Pneumonia	3 (0.5)	7 (2.3)
Bronchitis	2 (0.3)	1 (0.3)
Convulsion	1 (0.2)	1 (0.3)
Gastroenteritis shigella	2 (0.3)	0
Upper respiratory tract infection, bacterial	0	2 (0.7)

SOC = Standard of care.
[a] Reported by > 1 patient.

Steady-State Observed Trough Concentrations of Omalizumab and Total IgE in Pediatric and Adult Patients



Patients With Adverse Events by Baseline IgE

Study IA05

- No difference between treatment groups in AE frequency across baseline IgE level

Baseline IgE, IU/mL	Patients with AEs, n/N (%)	
	SOC + omalizumab	SOC + placebo
< 500	233/260 (89.6)	117/125 (93.6)
500 - 700	43/51 (84.3)	28/30 (93.3)
> 700	104/110 (94.5)	49/52 (94.2)

Adverse Events of Special Interest

- Malignancy
- Anaphylaxis

Pediatric Clinical Program—Malignancy

- Definition: any occurrence of malignant neoplasm in total pooled population
- No malignancy in omalizumab group
- Placebo group
  - 1 case of medulloblastoma in Study IA05
  - 1 case of nephroblastoma reported after end of trial

Pediatric Clinical Program—Anaphylaxis

- To identify reported cases, MEDRA terms "anaphylaxis" and "anaphylactoid reactions" Study IA05
  - 1 report of anaphylaxis to Demerol (omalizumab)
  - 1 report of anaphylaxis to nuts (placebo)

Summary of Pediatric Efficacy Data

- Reductions in exacerbations
- Fewer days requiring rescue medication
- Decreased systemic steroid burden
- Fewer hospitalizations

Summary of Pediatric Safety Data

- No meaningful differences in adverse events or serious adverse events
- No reports of malignancy in children treated with omalizumab
- 1 report of anaphylaxis in each treatment group (neither related to study drug)

Biological Plausibility of Potential Risk of Malignancy

Eva C. Guinan, MD

Associate Professor of Pediatrics, Harvard Medical School
Associate Director, Center for Clinical and Translational Research, Dana-Farber Cancer Institute

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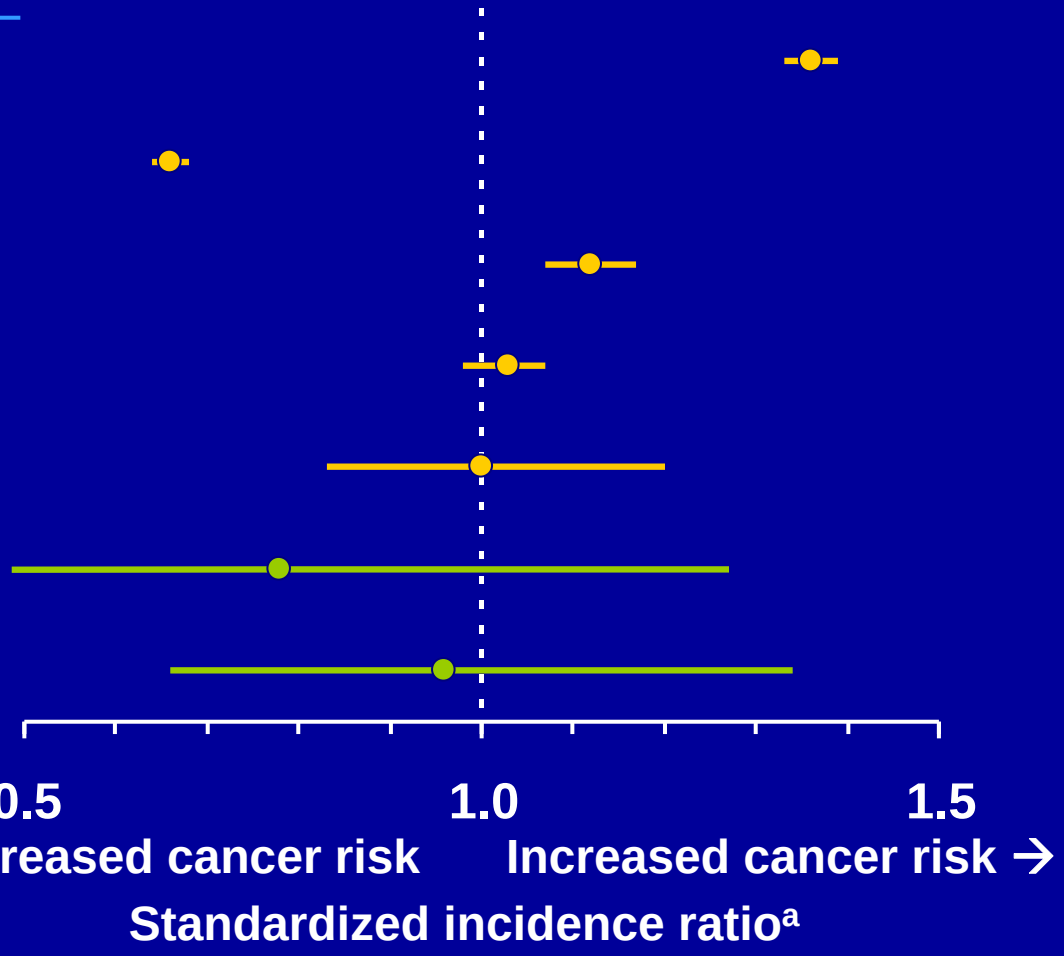
IgE Deficiency and Cancer

- 2 broad hypotheses have driven study of possible relationship between atopy and cancer
  - Atopy drives immune activation leading to increased surveillance and decreased malignancy risk
  - Atopy drives intrinsic and iatrogenic immune dysregulation and increased malignancy risk

Association of Asthma and Cancer Incidence—Summary of Cohort Studies

First author	Patients, n
Ji	140,425
Källén	64,346
Vesterinen (male)	35,126
Vesterinen (female)	42,826
Eriksson	6,224
Mills (male)	2,189
Mills (female)	



[a] Using general population as reference.

Relative Risk of Specific Cancers Among Asthmatic Patients

- Studies do not establish consistent effect on risk of specific cancers
  - Pediatric or adult malignancies
  - Adenocarcinomas, other solid tumors, and hematologic malignancies
  - Exceptions:
    - Increased incidence of lung cancer
    - Decreased incidence of glioma

IgE Deficiency and Cancer (1)

- Several studies compare IgE levels in cancer patients to control populations with variable results
  - IgE levels determined at time of, or after, diagnosis
  - Whether high/low IgE level antecedes diagnosis or contributes to carcinogenesis cannot be inferred
  - Melbye et al 2007[a] – IgE levels in banked samples from median 9 yrs prior vs at cancer diagnosis

[a] Melbye M, et al. *J Natl Cancer Inst*. 2007;99:158-166.

IgE Deficiency and Cancer (2)

- No reported primary relationship between IgE deficiency and cancer
  - No prospective studies of IgE levels and cancer incidence or cancer natural history
  - No data that pre-existing low or high IgE levels are associated with risk for, or freedom from, cancer

Deficiency of IgE in Otherwise Normal Populations

IgE deficiency is a common, naturally occurring state, with no published association with malignancy

- **IgE is generally not detectable in neonates**
- **A majority of humans remain IgE deficient for the first year of life**
- **In otherwise healthy individuals**
  - **Up to 10% of normal adults are IgE deficient[a,b]**
  - **Complete deficiency of IgE (< 2 IU/mL) is found in 4% of US Red Cross blood donors and 3.4% - 10% of healthy pregnant women[c,d]**

[a] Polmar SH, et al. *J Clin Invest*. 1972;51:326-330; [b] Levy DA, et al. *N Engl J Med*. 1970;283:541-542.
[c] Gleich GJ, et al. *J Lab Clin Med*. 1971;77:690-698; [d] Levin TA, et al. *Ann Allergy Asthma Immunol*. 2006;97:650-652.

IgE Deficiency and Cancer

- Hypogammaglobulinemia is seen as part of multiple pediatric syndromes of disordered immunity associated with increased malignancy rates
- All of these disorders have multiple immunologic/genetic cancer predisposition features
  - Common variable immunodeficiency can be associated with myelodysplasia
  - Ataxia telangiectasia (~ 60% IgE + IgA deficient) associated with NHL and GI malignancies (esp. upper)
  - Most common malignancy associated with immunodeficiency is lymphoma, particularly non-Hodgkin's lymphoma

Immunosuppression-Related Malignancy

- **Immunosuppression-related lymphoproliferative disease**
  - **Occurs with disease-related or iatrogenic immunosuppression**
  - **Stereotypical presentation preserved across etiologies**

    Mono-like syndrome → Oligoclonal → Monoclonal → Lymphoma
  - **Histology typically diffuse large B cell; frequent association with EBV**
  - **Likelihood is related to intensity of immunosuppression**
  - **Most often within 1 year of treatment**

EPV = Epstein-Barr virus.

Is Xolair Carcinogenic?

- Conservation of tumor type
  - Obvious cluster of tumor type or histology
  - Unusual tumor or subtype histology (sentinel diagnoses)
- Unusual epidemiologic features
  - Unusual age, site, or tumor behavior
- Acceleration of pre-existing neoplasia
  - Unusual patterns of recurrence
  - Distinctive temporal relationship to treatment
- Latency
  - For lymphoma, expected rate 1% - 10%/year
  - Other histologies longer

Summary

- No evidence that IgE influences cancer risk
- No evidence that normal populations with IgE deficiency have cancer predisposition
- Look for established patterns of disease
  - Patterns of malignancy mimicking congenital immunodeficiency states with concurrent hypogammaglobulinemia
  - Evidence of immunosuppression related lymphoproliferative disease
  - Presentations similar to other carcinogens

Xolair® (omalizumab) for Allergic Asthma in Pediatric Patients

Special Safety Topics and Risk Management

Linda Armstrong, MD

Executive Director
Drug Safety and Epidemiology
Novartis Pharmaceuticals Corporation

Genentech | NOVARTIS

Continued Risk Assessment

- Preclinical, clinical, and postmarketing data
  - Malignancy: potential risk
  - Cardiovascular/Cerebrovascular events: safety signal
  - Thrombocytopenia: potential risk
  - Anaphylaxis: identified risk
- Risks and potential risks identified in preclinical, adult and adolescent clinical, and postmarketing programs have not been observed in the pediatric clinical program

Overview

- Malignancy
  - Detection of potential risk
  - Risk management activities
- Cardiovascular and cerebrovascular events
  - Detection of potential risk
  - Risk management activities
- Thrombocytopenia
  - Preclinical observations
- Anaphylaxis
  - Detection of identified risk
  - Risk management activities

Malignancy
Phase I to III Studies in 2003 Adult Submission

- In clinical trials, malignant neoplasm were observed in 20 of 4127 (0.5%) omalizumab-treated patients compared with 5 of 2236 (0.2%) control patients
- Clinical data do not support association with omalizumab
  - Heterogeneous tumor cell types and organ origin not unexpected in this population
  - Brief latency period (60% < 6 mo)
  - Age of onset similar between control- and omalizumab-treated patients

Tumor Characteristics
Phase I to III Studies in 2003 Adult Submission

Malignant neoplasm	Omalizumab-treated patients, n n = 4127
Skin—nonmelanoma[a]	5
Breast	5
Prostate	2
Skin—melanoma	2
Parotid	1
Thyroid	1
Bladder	1
Non-Hodgkin's lymphoma	1
Pancreas	1
Rectum	1
Metastatic adenocystic parotid	1
Total	20 (21 cancers)

A patient is counted only once under each type of malignancy.
[a] 1 patient reported 4 events; 1 patient reported 2 events; each patient counted only once.

Patients With Malignancies by Exposure Interval

Phase I to III Studies in 2003 Adult Submission

Exposure interval, mo	Omalizumab n = 4127	Control n = 2236
0 - 3	6	1
3 - 6	6	3
6 - 9	3	1
9 - 12	3	0
12 - 15	2	0
Total	20	5

Mean age at diagnosis, yr (range)

- Omalizumab: 54 (30 - 75)
- Control: 50 (27 - 69)

[a] Malignancy rates per 1000 patient-years.

EXCELS Study Background

- Ongoing, prospective, observational cohort study
  - Primary objective long-term safety
  - Secondary objective effectiveness
- Approximately 5000 omalizumab-treated and 2500 usual care-treated patients
- No protocol-mandated treatment or random treatment allocation
- Five-year follow-up
- Patients may change therapy during study
- Study visits every 6 months
- Omalizumab patients seen every 2 - 4 weeks for drug administration

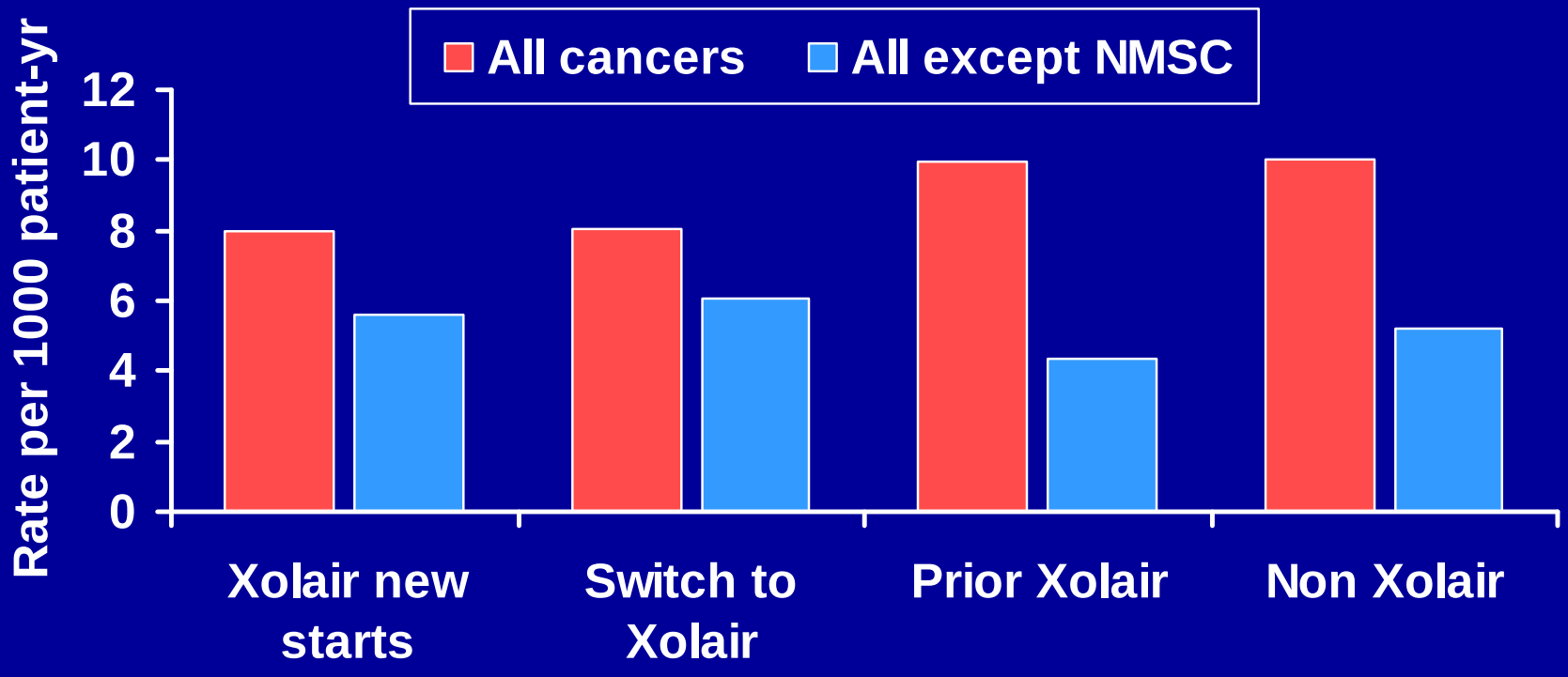
EXCELS—Confirmed Primary Malignancies at Last Interim Analysis

	Omalizumab cohort n = 5041	Non-omalizumab cohort n = 2886
Malignancy events, n	120	63
Person-yr at risk for any malignancy	12,313.4	6294.6
Mean duration of enrollment, yr	2.4	2.4
Observed malignancy rate (any type) per 1000 person-yr (95% CI)	9.83 (8.15, 11.74)	10.01 (7.69, 12.81)

Tables 14.3.1/17.1.1, 14.3.1/17.1.2

EXCELS—Incidence Rate of Cancer by Prior Exposure to Xolair®

- No significant difference in cancer incidence among patients with prior exposure to omalizumab compared to new starts and patients in the non-omalizumab cohort



Malignancy Spontaneous Reports 2004 - 2008

- Reporting proportion of malignancy has remained consistent since approval
- Majority of cases are nonmelanoma skin cancers and solid tumors in patients greater than 40 years of age
- Omalizumab exposure ranges from 6 days to 5.9 years

Malignancy Clinical Summary

- There is no pattern of malignancy mimicking pediatric immunodeficiency
- Evidence of immunosuppression-related lymphoproliferative disease has not been observed
- Tumors described do not suggest carcinogenicity
  - Tumor type, exposure duration, and age of onset do not support omalizumab causality

Malignancy
Risk Management Strategies

Current risk activities

- Malignancy warning included in USPI on June 20, 2003
- EXCELS Study

Proposed actions

- Targeted follow-up with the use of an event-specific questionnaire
- Background study: To understand the risk of cancer in asthmatic vs nonasthmatic pediatric population aged 6 to < 12 yr (eg, claims database analysis)
- Pediatric registry: To monitor the development of any malignant neoplasms in pediatric population

Overview

- Malignancy
  - Detection of potential risk
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- Cardiovascular and cerebrovascular events
  - Detection of potential risk
  - Risk management activities
- Thrombocytopenia
  - Preclinical observations
- Anaphylaxis
  - Detection of identified risk
  - Risk management activities

EXCELS Baseline Demographics

	Omalizumab n = 5041	Non-omalizumab n = 2886	All patients N = 7951
Asthma severity, n (%)			
Moderate	2537 (50)	2219 (77)	4766 (60)
Severe	2498 (50)	659 (23)	3167 (40)
Oral steroid use, n (%)	3626 (72)	1501 (52)	5143 (65)
Chronic	1219 (24)	311 (11)	1534 (19)
Periodic	2407 (48)	1190 (41)	3609 (46)
COPD, n (%)	393 (7.8)	161 (5.6)	557 (7.0)

- **In this non-randomized trial, the Xolair cohort included patients with more severe disease**

EXCELS Interim Study Report: Pre-Adjudication Cardiovascular/ Cerebrovascular Events

Events	Crude risk ratio (95% CI)	Omalizumab N = 5041	Non-omalizumab N = 2886
Global cardiovascular and cerebrovascular events	1.83 (1.3, 2.8)	131	40
Cardiovascular deaths	1.3 (0.5,4.7)	14[a]	6
Cardiac disorders	1.78 (1.1, 3.0)	83	26
Cerebrovascular disorders	2.96 (1, inf)	16	3
TIA	3.88 (0.7, inf)	7	1
Non-TIA	2.5 (0.6, inf)	9	2
Embolic, thrombotic, and thrombophlebitis	1.52 (0.9, 3.0)	49	18
Pulmonary hypertension	Undefined	6	0

[a] 2 additional events post-adjudication. TIA = Transient ischemic attack.

Cardiovascular and Cerebrovascular Events—Ongoing Evaluation

- Interim analysis of ongoing EXCELS study demonstrated a disproportionate increase in cardiovascular and cerebrovascular events
- EXCELS study continues with addition of prospective adjudication of cardiovascular, cerebrovascular and thromboembolic events
- Safety assessment is under evaluation and periodic updates have been provided

Overview

- Malignancy
  - Detection of potential risk
  - Risk management activities
- Cardiovascular and cerebrovascular events
  - Detection of potential risk
  - Risk management activities
- Thrombocytopenia
  - Preclinical observations
- Anaphylaxis
  - Detection of identified risk
  - Risk management activities

Platelet Observations—Preclinical Studies

- At supratherapeutic doses, decreased platelets were observed in juvenile cynomolgus monkeys
- Platelet effects were dose related and reversible with drug cessation
- Bone marrow platelet production normal, increased uptake of platelets by splenic macrophages
- No evidence of increased platelet activation or platelet lysis

Platelet Observations—Clinical Experience

- No evidence of drug-related thrombocytopenia in the adult and adolescent studies
- In postmarketing reports there were 6 spontaneous cases, 1 medically confirmed but not associated with hemorrhagic events
- In pediatric studies, intensive surveillance showed no evidence of acute reduction during first 5 wks of treatment
- Isolated low platelet counts observed in 6 omalizumab- and 1 placebo-treated patient
  - Repeat testing without intervention, on treatment, was normal

Platelet Summary

- Dose-related decrease in platelets observed in monkeys at supra-therapeutic doses
- Similar responses not observed in humans
- Postmarketing reports do not suggest an increased risk
- Results of preclinical studies described in Prescribing Information
- No additional risk mitigation activities warranted at this time

Overview

- Malignancy
  - Detection of potential risk
  - Risk management activities
- Cardiovascular and cerebrovascular events
  - Detection of potential risk
  - Risk management activities
- Thrombocytopenia
  - Preclinical observations
- Anaphylaxis
  - Detection of identified risk
  - Risk management activities

Anaphylaxis/Anaphylactoid Reactions
Controlled Clinical Trials

- Adult and adolescent program
  - 3 nonfatal reactions among 4265 omalizumab-treated patients
- Pediatric program
  - 1 non fatal reaction among 926 omalizumab-treated patients
- No fatal outcomes

Anaphylaxis Warning Added to Prescribing Information in 2007

- 57,300 patients treated June 2003 - December 2006
- Frequency of anaphylaxis was 0.2%
- Boxed Warning and Medication Guide added
  - Patients should be closely observed for an appropriate period of time after administration
  - Patients should be informed of the signs and symptoms of anaphylaxis, and instructed to seek immediate medical care should signs or symptoms occur
- Reporting proportion has remained constant since Warning added

Characteristics of Anaphylaxis in Spontaneous Reports Have Not Changed

- Reporting proportion remains at 0.2% since the addition of the Warning in 2007
  - The proportion requiring epinephrine has not increased
  - The proportion reporting emergency room treatment has not increased
  - No Xolair-attributed anaphylaxis fatalities

Anaphylaxis
Risk Management Strategies

Current activities

- Boxed Warning added to the USPI in 2007
- Risk Evaluation and Mitigation Strategy (REMS) approved July 2009
- Two postmarketing commitment studies (skin testing [completed] and prior history of anaphylaxis [ongoing])

Proposed actions

- Extension of REMS to pediatric patients
- Educational programs
- Surveys to measure effectiveness of risk minimization activities
- Targeted follow-up with the use of an event-specific questionnaire
- Expedited reporting of all cases of anaphylaxis

Xolair® Utilization in the United States

- Statement of medical need required for authorization
- Specialty pharmacies distribute to healthcare providers
- Administered by healthcare providers
- Limitations of Wolters Kluwer analysis (n = 5920)
  - 50% of specialty pharmacies do not contribute
  - Inability to consistently link specialty and retail pharmacies
  - List of concomitant medications not complete

Descriptions of Insurance-Based Claims Databases

- Specialty and retail pharmacy claims linked by unique patient identifier
- Complete drug list included

	AG Employer	i3	MarketScan	Healthcore
Time period	1999 - 2008	1997 - 2008	1996 - 2008	2004 - 2008
Data source	40 national large US employers	Over 45 health plans	45 large employers, health plans, government and public organizations	14 WellPoint health plans
Coverage	9+ million lives	86 million lives	18 million lives	31+ million lives
Key data elements	Eligibility records allowing longitudinal study design, medical claims (inpatient and outpatient services), and pharmacy claims			

Xolair® Use in Clinical Practice Insurance-Based Claims Databases

- **Asthma medication use during 2008 for all patients receiving Xolair between 1/1/2008 and 12/31/2008 with continuous eligibility during that time**

	Patients, %			
	AG Employer N = 590	i3[a] N = 1600	MarketScan N = 1793	Healthcore N = 949
Xolair + 2 or more classes	82.2	81.1	82.5	86
Xolair + 1 class	10.5	8.1	11.1	10
Xolair alone	7.3	10.7	6.4	5

[a] Asthma medication use during 2007 for all patients receiving Xolair between 1/1/2007 and 12/31/2007 with continuous eligibility during that time.

Conclusions

- Omalizumab has an extensive postmarketing experience with over 147,400 patient years
- The pediatric clinical program did not identify additional safety signals
- Novartis and Genentech are committed to monitoring the long-term safety of omalizumab in pediatric and adult populations
  - Risk management strategies have been established for identified risks
  - Additional activities are being developed to clarify potential risks

The Role of Omalizumab in the Treatment of Pediatric Moderate-to-Severe Persistent Allergic Asthma

Wayne Morgan, MD, CM

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Chief, Pediatric Pulmonary, Allergy, and Immunology
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Genentech | NOVARTIS

Key Considerations

- Asthma control is achievable in most children
- There remains a small population with moderate-to-severe persistent allergic asthma who are poorly controlled and suffer significant burden

Children with Uncontrolled Asthma Experience Significant Burden

- Symptoms
  - Frequent wheezing
  - Exercise limitation
  - Disrupted sleep
- Exacerbations
  - Systemic corticosteroids
  - Unscheduled urgent care/ED visits
  - Hospitalizations
- Potential long-term decline in lung function
- Mortality

The Impact of Frequent Exacerbation

- Interference with normal activity
- Risk associated with corticosteroid use
- Parents and caregivers

A Real World Patient—History

- 15-year-old male with uncontrolled asthma despite adherence to Advair® 500 @ 1 inhalation twice daily and Singulair® @ 10 mg po daily
- Frequent exacerbations with need for multiple prednisone bursts
- Favorite sport is rodeo and he can no longer work with animals due to his asthma
- Atopic with multiple environmental exposures including ranch and farm animals

A Real World Patient—Treatment

- Treatment with omalizumab resulted in improvement in asthma symptoms and reduced exacerbations
- Able to work with family's animals and participate in riding sports
- Elected to stop omalizumab after 8 months because he "didn't need it"
- Asthma became uncontrolled
- Treatment with omalizumab was resumed with an excellent outcome

Another Real World Example—History

- 10-year-old male with wheezing since his first year of life
- Atopic with seasonal worsening and no other comorbid conditions
- Environmental exposures include dust, wood smoke, and animals (dogs, horses, sheep)

Another Real World Example—Treatment

- His physicians have progressed his medication to
  - Advair® 500/50 @ 1 inhalation bid
  - Singulair® @ 5 mg po daily
- He is adherent to his care regimen and parents are knowledgeable
- He continues to have frequent day and night symptoms, frequent albuterol use
- Continues to have frequent exacerbations

Treatment Options

- Increase ICS
- Allergen immunotherapy
- Theophylline
- Alternate day prednisone

Conclusion

- Children with poorly controlled allergic asthma suffer significant burden
- Omalizumab reduces exacerbations in these children
- Omalizumab is an important therapeutic option

Supportive Slides

Dosing[a]
Study IA05

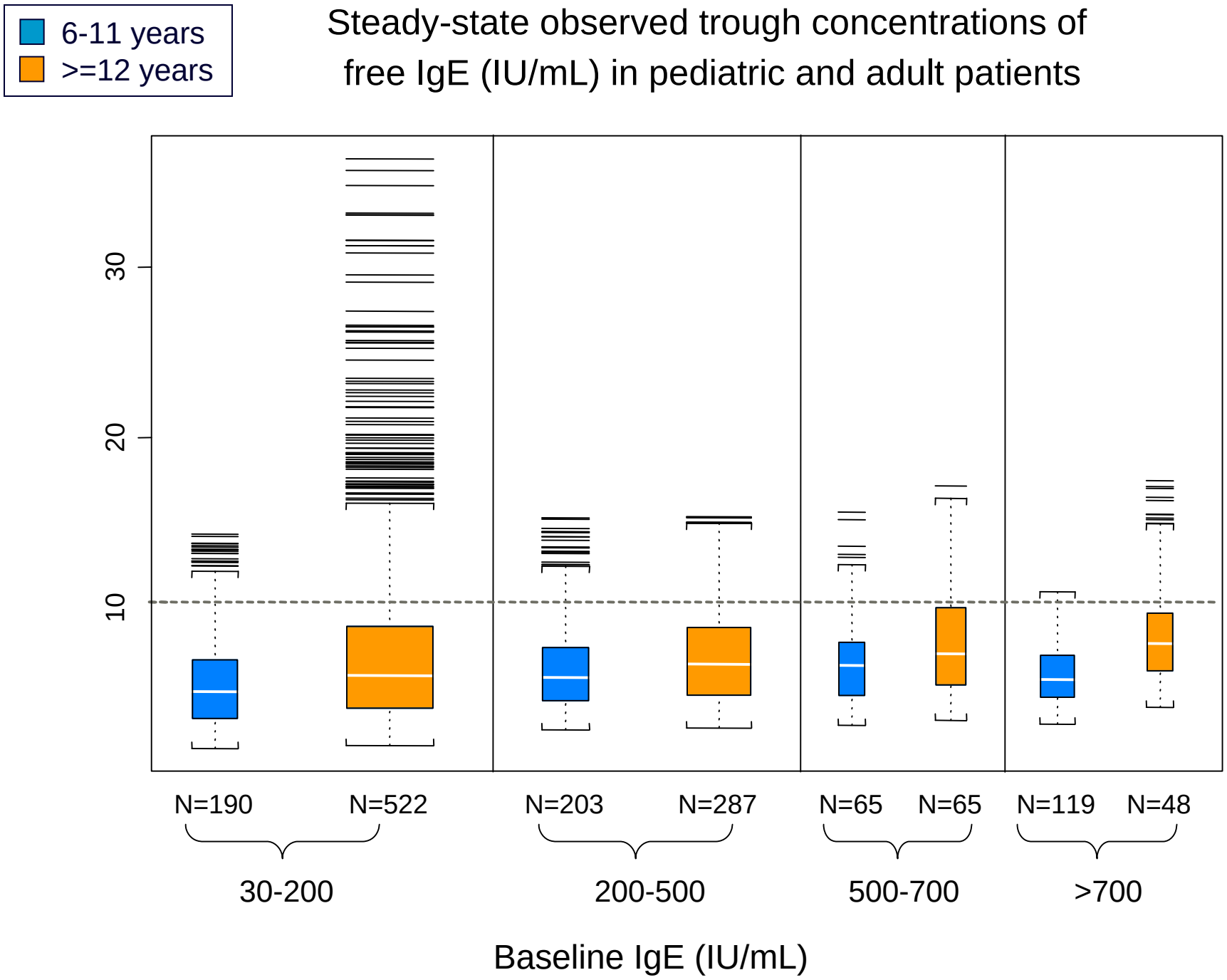
Dosing interval	Baseline IGE (IU/mL)	Body weight (kg)									
		20-25	>25-30	>30-40	>40-50	>50-60	>60-70	>70-80	>80-90	>90-125	>125-150
Q4wk	≥ 30 - 100	75	75	75	150	150	150	150	150	300	300
	> 100 - 200	150	150	150	300	300	300	300	300	225	300
	> 200 - 300	150	150	225	300	300	225	225	225	300	375
	> 300 - 400	225	225	300	225	225	225	300	300		
	> 400 - 500	225	300	225	225	300	300	375	375		
	> 500 - 600	300	300	225	300	300	375				
	> 600 - 700	300	225	225	300	375					
Q2wk	> 700 - 800	225	225	300	375	Do not dose in this area					
	> 800 - 900	225	225	300	375						
	> 900 - 1000	225	300	375							
	> 1000 - 1100	225	300	375							
	> 1100 - 1200	300	300								
	> 1200 - 1300	300	375								

[a] Dosing by mg.

Consistent Decrease of Exacerbations Across All IgE levels at Baseline at 52 Weeks

IgE at baseline	Omalizumab n = 384	Placebo n = 192	Rate ratio
IgE 0 - < 200	0.95	1.29	0.735 (0.467, 1.157)
IgE 200 - < 407	0.70	1. 15	0.609 (0.402, 0.921)
IgE 407 - < 726	0.82	1.43	0.572 (0.354, 0.925)
IgE = > 726	0.67	1.66	0.405 (0.246 ,0.666)

Steady-state observed trough concentrations of free IgE (IU/mL) in pediatric and adult patients



Limitations of Verispan SDI Health's Physician Drug And Diagnosis Audit

- Conclusion: Physicians indicated they were prescribing Xolair alone approximately 27% of the time
- Limitations
  - Sample included small numbers of Xolair prescribers
    - 0.9% of provider panelists are pulmonologists
    - 1.49% are allergists
  - Cross-sectional data collection does not capture drug use history
  - Potential missing data for patients seen by multiple providers
- Analysis of patient data may reduce the impact of these limitations.

Patient Assistance Programs

- The Sponsors assist in access to Xolair for those in need via:

1. Xolair Access Solutions

   Co-pay Assistance Programs

   - Assisting all eligible patients whose financial situations who may otherwise prevent them from accessing Xolair

   Genentech Access to Care Foundation

   - Established to help qualified patients with unmet medical needs who are uninsured or rendered uninsured by payer denial and who meet specific insurance, financial, and medical criteria to receive XOLAIR free of charge
   - Patient eligibility is contingent upon an income limit of $100,000

2. Xolair Debit Card Program
   - Eligible patients may have access to up to $1,500 over a period of 12 consecutive months to assist with their co-payment
3. Starter Program
   - Allows eligible patients to receive treatment while awaiting their insurance provider’s decision regarding coverage

Number (%) of Patients Receiving Each Dose and Regimen of Study Medication
Study IA05 Safety Population

	Patients, n (%)		
	SOC + omalizumab n = 421	SOC + placebo n = 207	Total N = 628
Dose and regimen			
75 mg every 4 weeks	34 (8.1)	24 (11.6)	58 (9.2)
150 mg every 4 weeks	77 (18.3)	36 (17.4)	113 (18.0)
225 mg every 4 weeks	42 (10.0)	17 (8.2)	59 (9.4)
300 mg every 4 weeks	79 (18.8)	46 (22.2)	125 (19.9)
225 mg every 2 weeks	89 (21.1)	41 (19.8)	130 (20.7)
300 mg every 2 weeks	62 (14.7)	24 (11.6)	86 (13.7)
375 mg every 2 weeks	38 (9.0)	19 (9.2)	57 (9.1)

Source: SCE-Table 14.3-1.3

Distribution of Patients According to the Dosing Table

Study IA05

Dosing: Q4W Q2W

Dosing range: Pediatric Adult

Baseline IgE, IU/mL	Body weight, kg										
	<20	20-25	>25-30	>30-40	>40-50	>50-60	>60-70	>70-80	>80-90	>90-125	>125-150
<30		1	2								
≥30-100		20	14	21	10	4	2	2			
>100-200		20	15	24	20	7	1	2			
>200-300		18	18	24	12	4	6	1		1	
>300-400		14	6	25	11	5	2				
>400-500		16	26	16	8	3	3	1	1		
>500-600		9	13	13	5	2	4				
>600-700		5	8	12	7	2					
>700-800	1	3	10	13	4	1					
>800-900		8	9	12	10						
>900-1000		13	8	12							
>1000-1100		4	4	12	1						
>1100-1200		10	9								
>1200-1300		8	5								
>1300		1	2	2							

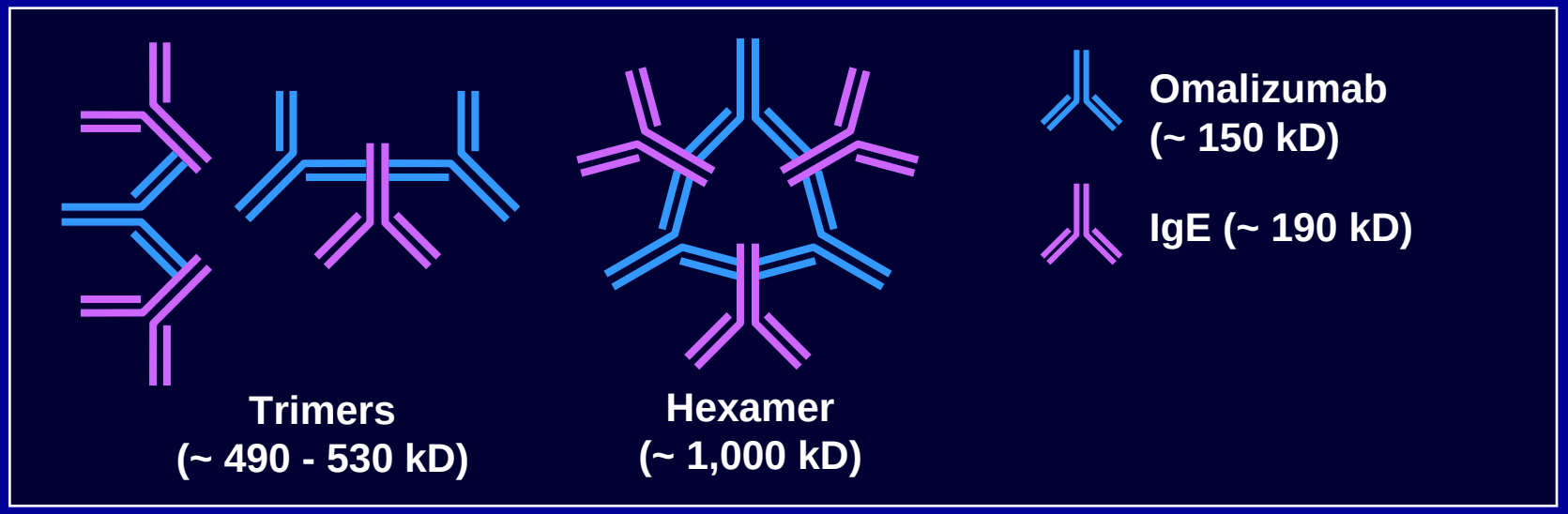
Do not dose

Do not dose

Patient Demographics—Race
Study IA05–Safety Population

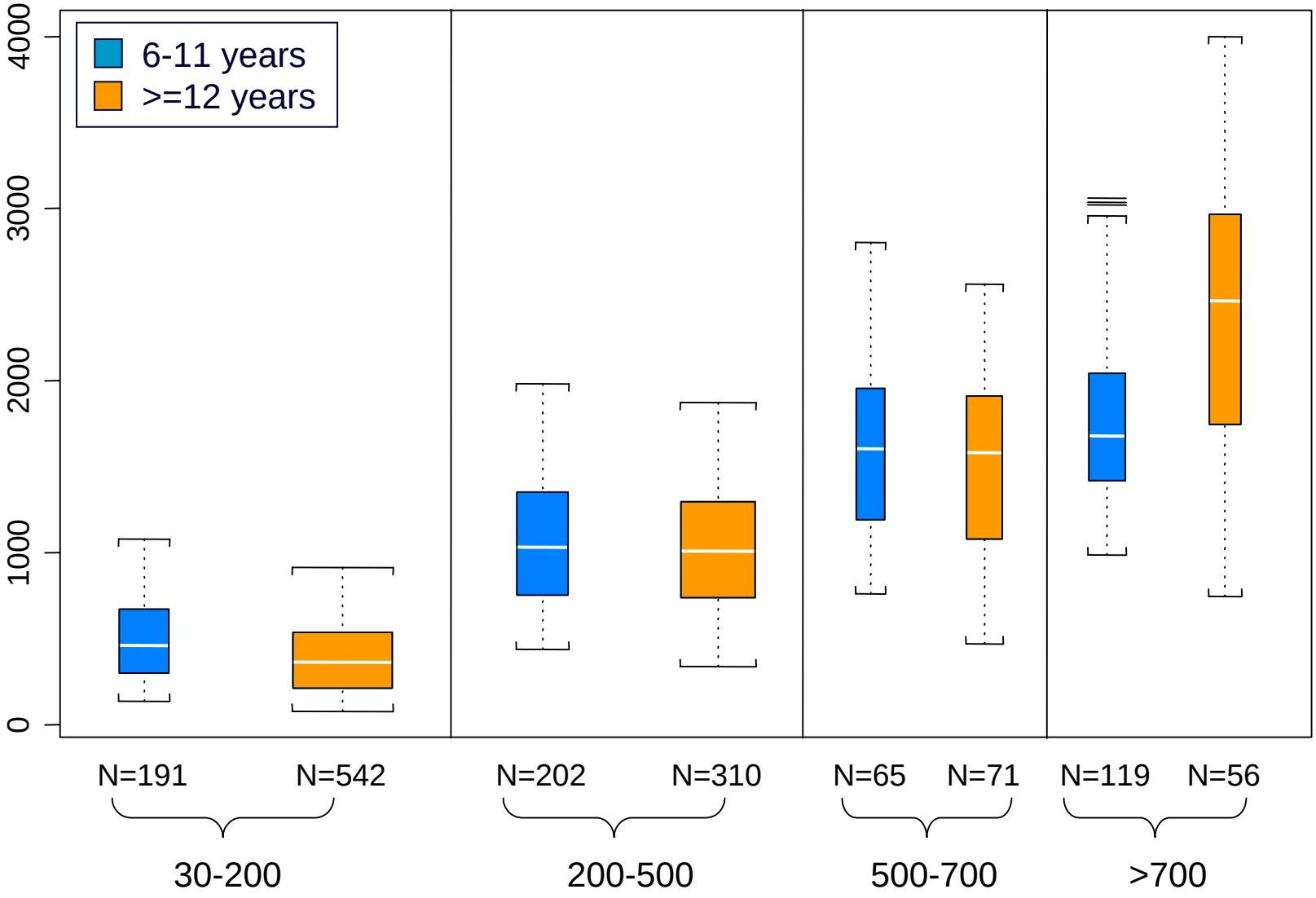
	SOC + omalizumab n = 421	SOC + placebo n = 207	Total N = 628
Race, n (%)			
Caucasian	249 (59.1)	128 (61.8)	377 (60.0)
Black	69 (16.4)	30 (14.5)	99 (15.8)
Oriental	0	2 (1.0)	2 (0.3)
Other	103 (24.5)	47 (22.7)	150 (23.9)

Omalizumab-IgE Complexes



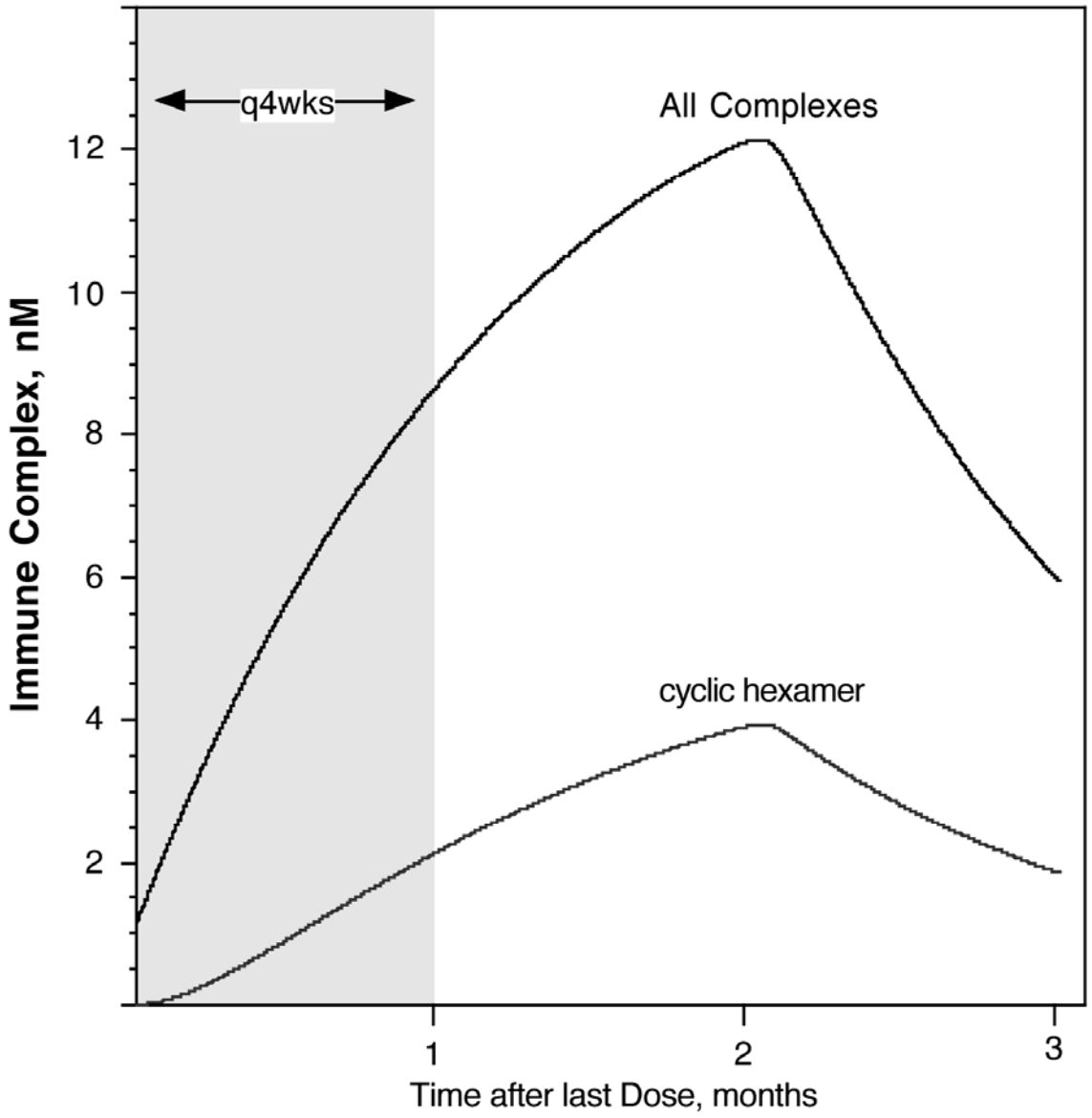
- Heterotrimers at omalizumab:IgE molar ratios > 1 (omalizumab excess) or < 1 (IgE excess)
- Hexamers at omalizumab:IgE molar ratios of ~ 1:1
- Complexes are small and present no safety risk

Steady-state observed trough concentrations of total IgE (IU/mL) in pediatric and adult patients

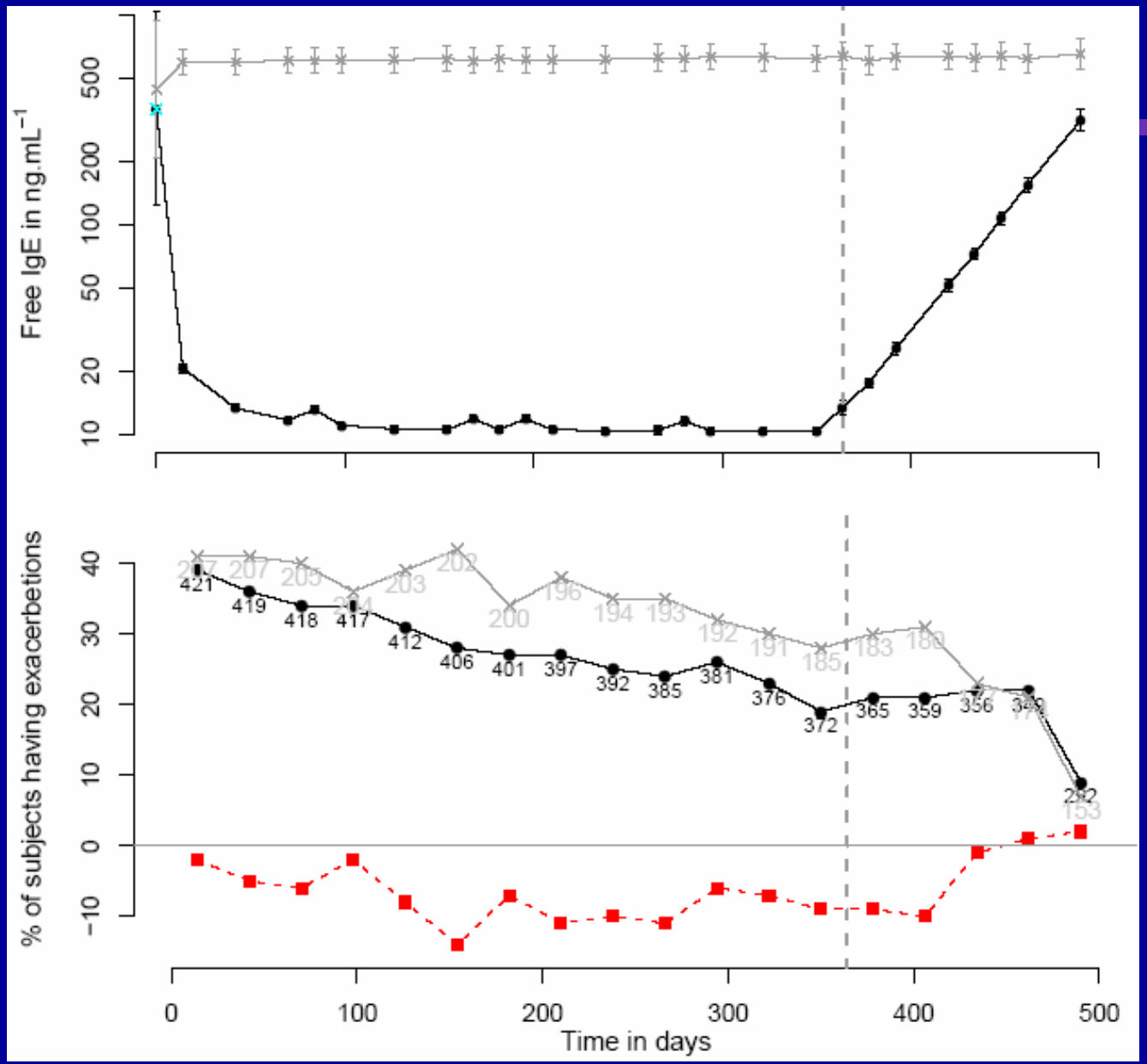


Dynamic Simulation of omalizumab:IgE Complexes:

Includes steady synthesis of new IgE and Loss of Complexes
IgE half-life of 3 days, IgG and Complex Half-life of 26 days



Free IgE and Probability of Exacerbation vs Time



- Exacerbation probabilities: mean values for 28-day observation periods (change from baseline).
- The number of subjects remaining in each study arm is shown.

Clinically Significant Asthma Exacerbations Using Poisson Regression by Treatment Period and Age Group

Study IA05—Modified ITT Population

	Omalizumab n = 384	Placebo n = 192
52-week fixed steroid treatment period		
Age: 6 - 9		
Total patients, n	229 (100.0)	131 (100.0)
Number of asthma exacerbations, n (%)		
0	125 (54.6)	56 (42.7)
1	50 (21.8)	25 (19.1)
2	29 (12.7)	20 (15.3)
3	12 (5.2)	12 (9.2)
≥ 4	13 (5.7)	18 (13.7)
Exacerbation rate during this treatment period	0.82	1.43
Ratio of exacerbation rates (95% CI)	0.574 (0.424, 0.777)	
p value for ratio	< 0.001	

Clinically Significant Asthma Exacerbations Using Poisson Regression by Treatment Period and Age Group

Study IA05—Modified ITT Population

	Omalizumab n = 384	Placebo n = 192
52-week fixed steroid treatment period		
Age: 10 - 11		
Total patients, n	155 (100.0)	61 (100.0)
Number of asthma exacerbations, n (%)		
0	78 (50.3)	20 (32.8)
1	46 (29.7)	22 (36.1)
2	11 (7.1)	7 (11.5)
3	12 (7.7)	3 (4.9)
≥ 4	8 (5.2)	9 (14.8)
Exacerbation rate during this treatment period	0.71	1.21
Ratio of exacerbation rates (95% CI)	0.585 (0.405, 0.845)	
p value for ratio	0.004	

American Academy of Allergy, Asthma and Immunology/American College of Allergy, Asthma and Immunology Joint Task Force: Recommendations on Omalizumab-Associated Anaphylaxis

- Informed consent should be obtained from patients after discussion of risks, benefits and alternatives
- Patients should be educated on signs and symptoms of anaphylaxis
- Patients and caregivers should be educated on use of epinephrine auto-injector and be advised to carry for 24 hours after administration
- An assessment of the current health status should be made prior to each injection
- Patients should be observed for 30 minutes after each injection and 2 hours for the first 3 injections—may be modified based on clinical judgment

Cox L, et al. *J Allergy Clin Immunol*. 2007;120:1373-1377.

Anaphylaxis Education Sheet

Treatment of anaphylaxis in the physician's office[1]	Treatment of anaphylaxis in the community[2]
Immediate measures	Patient self-management after leaving the physician's office
Assess airway breathing, circulation, and orientation	Information sheet on anaphylaxis with specific information on Xolair (omalizumab)
Inject epinephrine, 0.3 mg intramuscularly, in the vastus lateralis (lateral thigh)	Epinephrine autoinjector (EpiPen duopak or Twinject)
Activate emergency medical services (call 911 or local rescue squad)	Anaphylaxis Emergency Action Plan (downloadable from www.AAAAI.org)
Place patient in recumbent position and elevate the lower extremities, as tolerated	Anaphylaxis wallet card (available from www.AAAAI.org at no charge to members and minimal charge for nonmembers)
Establish and maintain airway	Medical identification jewelry tag (eg, MedicAlert bracelet)
Administer oxygen	
Establish an intravenous line for venous access and fluid replacement; keep open with normal saline	
Consider administration of nebulized albuterol, 2.5-5 mg in 3 mL of saline; repeat as necessary	
Consider administration of ancillary medications, such as H_1 antihistamine or a systemic corticosteroid	

Cox L et al J Allergy Clin Immunol 2007;120:1373-7)

Anaphylaxis Education Sheet

Treatment in the community

- Patient self-management after leaving physician's office
- Information sheet on anaphylaxis with specific information on Xolair (omalizumab)
- Epinephrine auto-injector (EpiPen duopak or Twinject)
- Anaphylaxis Emergency Action Plan (downloadable from www.AAAAI.org)
- Anaphylaxis wallet card (available from www.AAAAI.org at no charge to members and minimal charge for nonmembers)
- Medical identification jewelry tag (eg, MedicAlert bracelet)

Cox L, et al. *J Allergy Clin Immunol*. 2007;120:1373-1377.

Table 2-1 Post-marketing clinical studies

Study No.	Study Title	Study Status	Study Completion [b]	Number of Subjects to Date			
				Planned	Entered	Completed Study	Discontinued Study
Q3662g	A Phase IIIb Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of Omalizumab in Subjects with Moderate to Severe Persistent Asthma Who Are Inadequately Controlled with High-Dose Inhaled Corticosteroids and Long-Acting Beta Agonists (proportion with oral steroid use)	Ongoing	9/2009	850	850[a] Enrolled	675	175
Q2982g	A Prospective Randomized, Double-Blind Study of the Efficacy of Omalizumab in Atopic Asthmatics with Good Lung Capacity Who Remain Difficult to Treat (EXACT)	Ongoing	12/2011	300	145[a]	74	19
Q2948g	An Epidemiologic Study of Omalizumab: Evaluating Clinical Effectiveness and Long-Term Safety in Patients with Moderate to Severe Asthma (EXCELS)	Ongoing	12/2011	7500	7951 Enrolled	0	1738